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LECTURES ON THE HERTER FOUNDATION.[1]

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Lecture I.

SPIROCHAETOSIS.

Under the term "Spirochaetosis" are included those diseases of man and animals due to the spiral microorganisms known as spirochaetes. I shall confine myself to those which produce blood infection—the relapsing fevers—in which a remarkable periodic increase and decrease in the number of the spirochaetes is observable corresponding to alternating rises and falls of the host's body-temperature. Authority is divided as to whether the spirochaetes are protozoa or bacteria, and the matter is a fruitful theme of discussion upon which I shall not enter here. Judged, however, from their pathological effects and their prompt reactions to immune sera and certain drugs, they show a pronounced affinity to protozoa and exhibit phenomena not hitherto observed in bacteria.

As in trypanosomiasis, spirochaetosis is readily induced by inoculation with infected blood, and may thus be communicated almost indefinitely from animal to animal. In one series, for instance, I transmitted *S. duttoni*, with apparently undiminished virulence, through one hundred mice. Again, as in trypanosomiasis (*T. lewisi*, *T. evansi*), infection may take place by feeding.

[1] Delivered in the Medical Department of The Johns Hopkins University, October 8, 9, and 10, 1912.

Transmission of Spirochaetes by Arthropods.

Investigations conducted during the last few years have demonstrated conclusively that the blood-inhabiting spirochaetes are, in a number of instances, transmitted by blood-sucking arthropods, and I propose to deal chiefly with these results since they are of great practical importance to preventive medicine.

Spirochaetosis in Birds.

In the year 1891, Sacharoff, in the Transcaucasus, demonstrated that a spirochaete, called by him *Spirochaeta anserina*, was the cause of a very fatal epidemic disease in geese. The spirochaetes appeared in the birds' blood shortly before the onset of symptoms, multiplied enormously, and disappeared at the approach of death. He transmitted the disease to geese and fowls by inoculation. In the year 1903, Marchoux and Salimbeni, working in Brazil, observed a similar disease in fowls, and since that date fowl spirochaetosis has been recorded from many parts of the world, the causative agent being now generally known as *Spirochaeta gallinarum*. We know to-day that spirochaetosis in fowls occurs in South-eastern Europe, in Asia, Africa, South America and Australia, and, in all places where the disease exists, is found what Marchoux and Salimbeni were the first to show to be the carrier, the tick, *Argas persicus* (Fig. 1). I have seen blood-films and determined the tick from many different places

where the disease has been recorded. Personally, there is no longer any doubt in my mind as to the identity of *S. anserina* Sacharoff and *S. gallinarum*. *Argas persicus* has accompanied the fowl in its distribution in many parts of the world, but the fowl has got rid of the pest in colder climates as the tick is unable to develop at low temperatures.

Spirochætosis in fowls is a very fatal febrile disease; the mortality in a yard may attain 40-100 per cent. The disease begins with diarrhœa, followed by loss of appetite and somnolence. The birds' feathers appear ruffled, the comb pale, the birds cease to perch, and, as the disease advances, they lie prostrate upon the ground. Death may take place suddenly during a convulsive attack. The disease occurs at times in a chronic form, the emaciated birds developing paralytic symptoms after apparent recovery. Death takes place in anywhere from 3 to 15 or more days, according to the type of the disease, the body-temperature at the time of death being frequently subnormal. Whereas, in chronic cases,

Fig. 1.—*Argas persicus* ♀.

the liver and spleen appear atrophied, these organs are much enlarged in acute cases, the liver showing fatty degeneration and at times focal necroses. The fowl spirochæte from Brazil kills geese in 5 to 6 days after inoculation, and produces a fatal infection in ducks, guinea-fowls, turtle-doves, and other birds.

Thanks to the kindness of Dr. Marchoux, I was able, at an early date, to confirm his and Salimbeni's results with infected *Argas persicus* (=*miniatus*) which he sent me from Brazil. Since that date Marchoux, Borrel, and others, also Hindle, in my laboratory, have materially advanced our knowledge of the mechanism whereby the tick infects the fowl. Without wearying you with the details of each experimenter's work, I may summarize it as follows:

The ticks are best rendered infective if they are maintained at a temperature of 30-35° C. after they have fed upon blood containing the spirochæte. If kept at a low temperature, 15-18° C., the spirochætes disappear very soon from their alimentary tract, and the ticks may bite birds repeatedly without infecting them. They may, however, be rendered infective after three months if placed at 30-35° C.; the spirochætes then reappear in their coelomic cavity, as may be shown by cutting off one of the tick's legs and examining the coelomic fluid which exudes from it upon a slide.

When the spirochætes first enter the tick they soon disappear from the gut, a certain number degenerate, whilst others

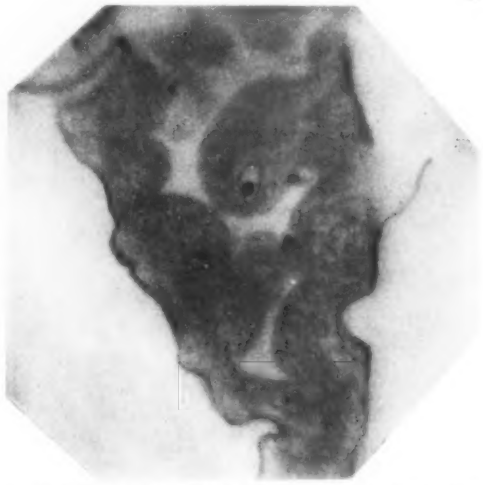

Fig. 2.—*Argas persicus*. Section of uninfected tick's Malpighian tubule. (E. Hindle.)

traverse the gut wall and enter the coelomic cavity to circulate all over the body. A number of them die in this situation as evidenced by the frequent presence in the coelomic fluid of pale, scarcely visible, non-motile spirochætes which are difficult to stain. The spirochætes next enter the various

Fig. 3.—*Argas persicus*. Section of heavily infected Malpighian tubule. The cells are filled with agglomerations of coccoid bodies. (*Spirochæta gallinarum*.)

organs, especially the cells of the Malpighian tubules and sexual organs, in which they break up into a large number of small particles, or coccoid bodies, which multiply by fission and give rise to large agglomerations which can be seen very distinctly in stained specimens (Heidenhain stain).[2] The

[2] Compare Figs. 2 and 3.

coccoid bodies may also be found within the lumen of the gut and Malpighian tubules and in the excreta. In the act of feeding, the tick occasionally voids excrement and exudes a few drops of secretion from coxal glands situated in the first intercoxal space, the fluid pouring out of a wide duct and being rapidly secreted from the freshly imbibed blood serum. This fluid, as well as the salivary and intestinal secretion of *Argas*, contains an anticoagulin, as I showed with Strickland.

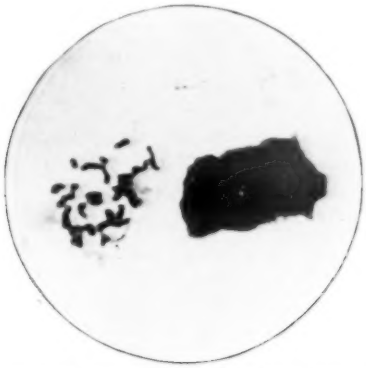

FIG. 4.—*Argas persicus*. Smear of infected ovum of the tick incubated 24 hrs. at 37° C. Coccoid bodies, in a Malpighian cell, developing into spirochaetes. (E. Hindle & B. G. Clarke phot.)

The coxal fluid dilutes the escaped excrement and facilitates its getting into the wound inflicted by the tick. This is doubtless the usual mode of infection, the coccoid bodies in the excrement gaining access to the blood of the host and afterwards developing into spirochaetes, though the latter development has not actually been followed. Marchoux and Couvy (1912) state that infection may, however, take place without coxal secretion being voided. The bird begins to show

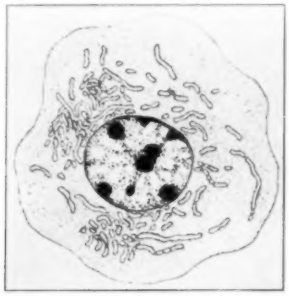

FIG. 5.—*Argas persicus*. Drawing of Malpighian tube cell of embryonic tick maintained 5 days at 37° C. showing coccoid bodies (S. gallinarum) developing with spirochaetes. (E. Hindle, 1911.)

symptoms after a period of incubation of about four days following upon the bite of the infected tick.

Although it was denied that the spirochaete of the fowl is transmitted hereditarily to the offspring of *A. persicus*, I expressed the opinion some years ago[5] that there was every probability that it would be found to be transmitted hereditarily as is *S. duttoni* in *Ornithodorus moubata*. Hindle has recently confirmed this supposition (Figs. 4 and 5). Coccoid bodies are found within the Malpighian cells of the embryonic tick, as described by Leishman for *S. duttoni* in *O. moubata*. If the eggs are maintained at 37° C., the coccoid bodies grow out and assume a form which suggests they are on the way to forming spirochaetes. The spirochaete stage occurs in the coelomic fluid of the tick, but not within its body cells. I may add here that *Argus reflexus* has been shown by Shellack (1908) to transmit the fowl spirochaete.

[5] Harben Lectures, 1908.

HUMAN RELAPSING FEVER IN TROPICAL AFRICA.

Although David Livingstone (1857) was the first to report upon pathogenic effects following upon the bite of the tick we know to-day as *Ornithodorus moubata* (Fig. 6), it was not until the year 1905 that Dutton and Todd, in the Congo, and shortly afterwards, Robert Koch, in German East Africa, demonstrated that this tick transmitted spirochaetosis to man. The British authors made the important observation that the *Spirochaeta duttoni* is transmitted hereditarily to the offspring of the tick, a fact confirmed by Koch, who discovered that 5-15 per cent, and at times 50 per cent, of the ticks harboured the parasite. Koch captured the ticks at resting

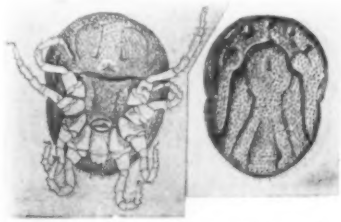

FIG. 6.—*Ornithodorus moubata* ♀.

places along caravan routes and in places outside the regular routes. Apparently, owing to German East Africa having been opened to trade for a much longer period than the Congo, the tick appears to be much more widely distributed in East Africa than in the Congo. Dutton and Todd state that in the Congo it only occurs along routes of travel. I have examined a large number of specimens of this tick from various parts of Africa and would note that its geographical distribution is far wider than our present records show for the distribution of relapsing fever in man. There is every reason to fear, therefore, that an extension of the disease will follow with time, unless the natives learn even better than they do to shun the "tampan." In fact, I have an interesting observation to note in this connection which bears out my contention. It emanates from the Rev. John Roscoe, of Cambridge, who gave me the information last year. This gentleman was a missionary in Uganda, where he lived for many years at Kampala in a native-built house having reed walls supported by the usual wooden pillars. To quote his words: "Some of the pillars were in rooms, not in the walls, and it was at the bases of two of these pillars in the room used as a dining room that I noticed the ticks in the year 1896 or about that time. For several years I continued to live in the same house and suffered no harm from them. In more recent years, that

is, about 1903 or 1904, both Europeans and natives have suffered from "Tick Fever" (Spirillum) in houses which were built on either side of the site on which my old house stood. It has been affirmed that the ticks in these houses are the cause of the fever; I can only conclude that in previous years they were innocuous and that they have become noxious since 1896." I do not know of any similar observation having as yet been recorded.

The disease has repeatedly been transmitted to experimental animals, rats, mice, and monkeys, by means of infected ticks, and in a number of cases unwittingly to experimenters in European laboratories. I may, in this connection, instance the case of Mr. Merriman, in my laboratory, who suffered from the disease in consequence of being bitten by two *O. moubata* (first-stage nymphs) whose biology he was studying. He did not know he had been bitten by the ticks until after two days when he showed me two characteristic bites upon his forearm. His attack followed 16 days after the bites were inflicted, the incubation period being four to six days longer than is usual.

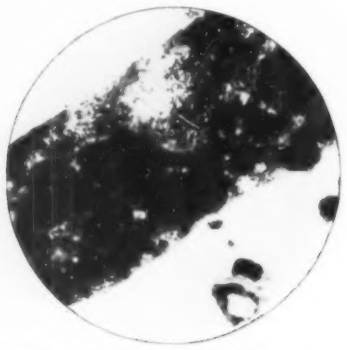

FIG. 7.—*Ornithodorus moubata.* Malpighian tube of 3d stage nymph infected hereditarily with *Spirochaeta duttoni.* A vast number of coccoid bodies fill the malpighian cells. (Sir Wm. Leishman.)

Of 25 monkeys with which Möllers experimented in Berlin no less than 20 died of spirochaetosis. There is, therefore, no possible doubt about the tick being the carrier of the disease.

Möllers' observations were of fundamental importance in relation to the etiology of the disease. He proved that ticks continue to harbour the parasite even after repeated feeds upon clean animals: thus 10 out of 12 monkeys were infected in succession by one lot of ticks which were fed upon them. His stock of ticks had died down to a low point toward the end of the series or the positive results would doubtless have continued longer. A tick may remain infective for 18 months or more after its initial infective meal of blood. He proved, moreover, that the parasites in the tick were transmitted hereditarily to the third generation when the ticks were fed throughout upon clean animals. Another observation possessing considerable interest is that of Manteufel (1910) that the ticks apparently acquire immunity to spirochaetal infection. Hindle has since found that about 30 per cent of the *moubata* sent to me from Uganda failed to become infected. It is conceivable that the stage of the disease or of the spirochaete's development at which the tick imbibes the parasites may have some influence upon the number of ticks which become infected, as noted by Miss Muriel Robertson for *Trypanosoma gambiense* in *Glossina palpalis*, to which reference will be made in the next lecture. Such a condition might well account for some of the immunity which is stated to occur. We know that there are marked variations in the viability of spirochaetes in relapsing fever blood preserved in vitro. Thus, Novy and Knapp (1906) found that *S. recurrentis* (American strain) survived for 30 to 40 days in defibrinated blood drawn from a rat during the onset of the disease, whereas they only survived 24 hours in blood drawn during the decline.

Although Dutton and Todd, Balfour, and others observed the breaking up of spirochaetes into minute granules in the body of ticks, Leishman was the first to follow the process more clearly. He proved that the coxal secretion was anticoagulant and non-infective, and that the excreta were infective by inoculating them into animals. He found that only

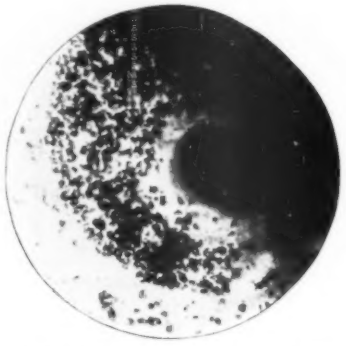

FIG. 8.—*Ornithodorus moubata.* Egg protruding from edge of ovary of infected female and heavily charged with coccoid bodies × 1500. (Sir Wm. Leishman.)

when *moubata* voided excreta in the act of biting that animals under experiment became infected. He therefore concluded that the mode of infection is contaminative through the tick's excreta, and not active through its proboscis. Experiments which I carried out, and which were extended and reported upon by Hindle in my laboratory, completely confirm the results of Leishman. If the internal organs of an infected *moubata* are carefully dissected out and well washed in sterile salt solution, it is found that the gut, together with its contents, the Malpighian tubes, the sexual organs and excrement are infective when emulsified and injected into a susceptible animal. The coxal secretion always, and the salivary glands in most cases, give negative results. The few positive results with salivary gland inoculations may well be referred to experimental error in that the glands, in the process of dissection, may easily become contaminated by spirochaetes derived from other organs and be imperfectly cleansed in the process of washing. Inoculations with emulsified eggs of *moubata* have also given positive results as might be expected for spirochaetes have been found in them by a number of

authors. Koch (1905) and Carter (1907) being among the first to demonstrate their presence microscopically in this situation.

After being ingested by the tick, the spirochaetes usually disappear from the lumen of the gut in about nine to ten days, but they reappear if the tick is placed at 35° C. They are then found in the coelomic fluid and their subsequent behaviour is similar to that described in the fowl spirochaete (Figs. 7 and 8).

It is highly probable that other species of *Ornithodorus* play a like part in the etiology of relapsing fever in other parts of the world than those in which *moubata* occurs, the latter being a purely African species. *Ornithodorus savignyi*, which is indistinguishable from *moubata* at a casual glance, and which also occurs in Africa, at Aden, and in India, has been found by Brumpt to convey a spirochaete derived from cases of human relapsing fever occurring in Abyssinia. *Ornithodorus turicata* is suspected in connection with relapsing fever in Colombia and *O. talaje*, I have no doubt, might play a similar part in Mexico and Central America whence I have received specimens. Lately, both Leishman and myself have received specimens of *O. tholozani* from Quetta, India, where it was suspected of being a vector, but experiments carried out with the few living examples which reached Leishman have proved negative. Again, from the fact that *Argas persicus*, as tested experimentally by Sergent and Foley (1908) in the Sud-Oranais, Africa, serves as a host for spirochaetes of human origin, we may conclude that this species, which frequently attacks man, may also communicate relapsing fever under suitable conditions. Sergent and Foley found the spirochaetes present in the coelomic fluid of this tick for two days, after which they disappeared.

That neither the tick nor the spirochaete are specifically adapted to each other is a matter of considerable importance which has been revealed by recent research. In view of the morphological similarity of the supposedly different species of spirochaetes and their individual variations in virulence, we may well doubt if many of the "species" are valid. As I pointed out four years ago, the various specific names given to the spirochaetes causing relapsing fever in man may be used merely for convenience *to distinguish strains or races* of different origin.[1] They cannot be regarded as valid names, in the sense of scientific nomenclature, for virulence and immunity reactions are not adequate tests of specificity. Under experimental conditions *O. moubata* has served for the transmission not only of *S. duttoni* and two other so-called species, *S. recurrentis* and *S. novyi*, which affect man in the Old and New World respectively, but it has also been found to transmit the fowl spirochaete. *S. duttoni*, moreover, has been successfully transmitted to rats by *Haematopinus spinulosus*, the common rat-louse. There is every reason to suppose that a spirochaete capable of adapting itself either to a tropical African tick or to a rat-louse occurring all over the world, will be able to accommodate itself to a variety of vertebrate hosts; and we know in fact, from laboratory tests, that a considerable number of animals are susceptible to infection with *S. duttoni*, various species of monkeys, rats, mice, rabbits, guinea-pigs, sheep, goats, horses, and dogs, etc., having been successfully infected.

[1] *S. recurrentis* may be the only true species; the name *recurrentis* has priority over *S. obermeieri*. Other so-called species are *duttoni*, *rossi* or *kochi*, *novyi*, *berbera*, *carteri*, etc.

Transmission of Relapsing Fever by Pediculus and Cimex.

It has long been supposed that vermin are responsible for the transmission of relapsing fever in Europe. Flügge (1891) appears to have been the first scientific writer to suggest this possibility, and Tictin (1897) supposed that bugs (*Cimex lectularius*) might transmit the disease by their bites or by being crushed and their contents entering the skin through excoriations due to scratching. He infected monkeys with the contents of bugs removed 24 hours after they had fed on relapsing fever blood. Karlinski (1902) and likewise Schaudinn observed the survival of spirochaetes in bugs for 30 days or more. Christy (1902) and Breinl, Kinghorn, and Todd (1906) failed to transmit spirochaetosis by bugs. In experiments of my own (1907) it was found that *S. duttoni* survived six days in the bug at 12° C., but only for six hours at 20-24° C. Similar results were obtained by *S. recurrentis* (from Russia). The parasites appeared to be merely digested by the bug, the rate of digestion being governed by the temperature at which the insects were maintained. In but one experiment did I succeed in transmitting relapsing fever to a mouse by means of bugs. In this case I used 35 of the insects, and transferred them directly from an infected to an uninfected mouse, interrupting their feed upon the first animal and allowing them to complete it upon a second clean mouse. We may, therefore, conclude that bugs can occasionally transmit relapsing fever.

We have, on the other hand, conclusive proof that lice are concerned in the transmission of the disease. The first important evidence in this connection dates from Mackie (1907), in India. This author records an outbreak of relapsing fever amongst school children, in which 137 out of 170 boys and 35 out of 114 girls, were attacked. The boys were found to be more infested with vermin than were the girls. An examination of the lice removed from the boys showed 24 per cent of them to contain spirochaetes, whereas only 3 per cent of the lice collected from the girls contained these microorganisms. As the epidemic increased among the girls their verminous condition became more evident, as the epidemic decreased among the boys the lice were found less frequently upon them. Mackie noted that the spirochaetes multiplied within the gut of the lice and that they could be found in the ovary, testis, and Malpighian tubules of the insects. He concluded that infection might result from the insects regurgitating the contents of their alimentary canal into the wound in the act of feeding.

Sergent and Foley (1908) next observed the presence of *Pediculus vestimenti* upon the persons of nearly all patients affected with relapsing fever in Sud-Oranais, North Africa,

and they observed spirochaetes in the bodies of the lice. Subsequently (1910), they found these lice associated with every case they observed in Algeria.

The most convincing observations are, however, those published in a short paper this year by Nicolle, Blaizot, and Conseil (1912). They note, in respect to its epidemiology, that relapsing fever affords a striking similarity to typhus fever. The disease extends in a similar manner, it occurs in the same places, when it enters hospitals it does not spread, sparing the nurses and physicians who have to deal with the patients who have been cleansed, whereas it attacks those who have to handle the patients at their entry into the hospital. In both diseases, as observed in Tunisia, lice are invariably found on the patients.

Nicolle and his colleagues obtained negative results when they attempted to transmit the disease through the *bites* of infected lice placed upon experimental monkeys and five persons (two of whom were the authors), although both men and monkeys were exposed to thousands of bites collectively. Upon studying the behaviour of the spirochaetes in the lice (*P. vestimenti* and *P. capitis*), they found that they disappear and afterwards reappear. But few can be detected in the gut five to six hours after the infective feed, and none are discoverable microscopically when 24 hours have elapsed. After about 8 to 12 days, however, actively motile spirochaetes reappear in the louse; at first they are short, but later they resemble those seen in the blood. Such spirochaetes are observable in lice up to the 11th day, and possibly longer. Monkeys inoculated with the contents of lice, crushed on the 15th day after the infective feed, developed relapsing fever.

We know that all persons infested with lice are addicted to scratching themselves, whereby they excoriate their skin and frequently crush the lice upon their bodies. In this manner their hands and finger-nails become infected with the body contents of the lice including the spirochaetes, and these gain a ready entrance through the excoriated skin, thereby infecting the individual. One of the authors, having excoriated his skin, smeared the contents of an infected louse upon the lesion, and succeeded thereby in infecting himself, the disease developing after a period of incubation lasting five days. In one experiment, infection followed the placing of the contents of a louse upon the conjunctiva in man. In nature, it might well happen that the soiled hand might travel to the eye and produce infection in a similar manner. The authors proved, moreover, that the spirochaetes are transmitted hereditarily to the offspring of the infected lice, for they found that eggs, laid 12 to 20 days after the infection of the parent lice, contained the spirochaete. The larvæ issuing from these eggs likewise contained spirochaetes. By incubating the eggs at 28° C., the larvæ hatched out on about the seventh day. When the eggs or larvæ were crushed and inoculated into a monkey the latter became infected.

We still lack detailed information regarding the behaviour of the spirochaetes in the lice and their offspring; possibly it is similar to that recorded for *S. duttoni* in *O. moubata*. The main point may, however, be now regarded as established that lice (both *P. vestimenti* and *P. capitis*) transmit relapsing fever and are presumably the ordinary vectors in most parts of the world. These discoveries are naturally of the greatest practical importance, in view of the prevention of relapsing fever.

I shall here digress to say a few words about the biology of lice infesting man, since you will find no precise information about it in the literature, except for the observations made by my demonstrator, Mr. Cecil Warburton, in Cambridge. The latter has made the only accurate observations hitherto recorded for *Pediculus vestimenti* in conjunction with an investigation we undertook on behalf of the Local Government Board, the results of which were published in their reports for 1910. Mr. Warburton found that *P. vestimenti* (=*corporis*) lives longer than *P. capitis* under adverse conditions. This is doubtless due to its living habitually on the clothing, whereas *capitis* lives upon the head where it has more frequent opportunities of feeding. He reared a single female upon his own person with self-sacrificing enthusiasm, keeping the louse enclosed in a cotton-plugged tube with a particle of cloth to which it could cling. The tube was kept next to his body, thus simulating the natural conditions of warmth and moisture under which these creatures thrive. The louse was fed twice daily whilst it clung to the cloth upon which it rested. The female lived one month. She copulated repeatedly with a male which died on the 17th day, and was replaced by a second male which likewise entered into copulation and survived the female. Copulation commenced five days after the female emerged and the process was repeated a number of times, sexual union lasting for hours. The female laid 124 eggs within 25 days. The eggs hatched after eight days under favourable conditions, such as those under which the female was kept; they did not hatch in the cold. Eggs kept near the person during the day and hung in clothing by the bedside during the winter in a cold room, did not hatch until the 35th day. When the larvæ emerge from the egg they feed at once if given a chance to do so. They are prone to scatter upon the person and abandon the fragment of cloth to which the adult clings. The adult stage is reached on the 11th day after three moults occurring about every fourth day. Adults enter into copulation five days after the last ecdysis. The adults reared by Mr. Warburton lived about three weeks after the final moult, and the "egg to egg" period is reckoned at about 24 days. Unfed *P. vestimenti* adults died quickly at any temperature; only one specimen survived in a feeble condition until the fifth day. Unfed larvæ died in 36 hours.

To this we may add that Nicolle and his colleagues find that both *P. vestimenti* and *P. capitis* survive longest when maintained at 28° C., in a damp atmosphere, being fed twice a day.

I have allowed myself this digression, dealing with *Pediculi*, because Warburton's results are doubtless unknown to many and these parasites have only lately crept—not sprung—into prominence especially with regard to the etiology of typhus fever and relapsing fever.

It is of importance to note how long the eggs may survive in view of the hereditary transmission of the spirochaetes in lice. It is obvious that the disinfection of verminous clothing is indicated as a preventive measure, and that those coming in contact with patients suffering from these diseases should promptly change their clothing and inspect their persons carefully after exposure with a view to avoiding the bites of infected lice.

SPIROCHAETOSIS IN CATTLE.

The discovery of spirochaetosis in cattle is due to Theiler after whom the causative agent, *S. theileri*, has been named. The parasite is transmitted by the tick *Boophilus decoloratus* in Africa (Fig. 9). Laveran and Vallée, to whom Theiler sent the infective ticks, reproduced the disease experimentally in France. That the ticks in this case become infected hereditarily goes without saying, for the infective ticks used by the French authors were larvæ hatched from eggs laid by females

FIG. 9.—*Boophilus decoloratus*, ovipositing females.

which had fed on cattle harbouring the spirochaetes in South Africa. We lack observations to show if the ticks may remain continuously infective through several generations, as seen in *S. duttoni*-infected *O. moubata*. About 14 days after such infective larvæ are placed upon cattle, the latter develop spirochaetosis, but the infection appears to be mild. In Laveran and Vallée's experiment spirochaetes were only present in the blood for four days. Four days later, however, the animal developed piroplasmosis, proving that the ticks had transmitted a double infection. Koch, working in Africa in the same year (1905), likewise observed spirochaetosis in cattle and reported finding the spirochaetes in the eggs of a species of tick which he found upon the affected animals.

This exhausts the list of spirochaetes concerning whose mode of conveyance we have definite knowledge. There are, however, a number of different animals infected by spirochaetes which are doubtless transmitted in a similar manner. Horses occasionally harbour spirochaetes, and so do sheep in Africa, and, judging from inoculation experiments, these spirochaetes are probably identical with *S. theileri*. Bats, as Nicolle and Comte found in Northern Africa, suffer from a typical relapsing fever due to *S. vespertilionis* which may be conveyed by several of the numerous ectoparasites infesting these animals; *Argas vespertilionis* and lice would naturally suggest themselves to me as being the probable vectors. *Spirochaeta muris*, occurring in rats and mice, and *S. gondi* Nicolle, 1907, occurring in a small African rodent (*Ctenodactylus gundi*) are both transmissible by blood inoculation and presumably in nature are transmitted by ectoparasitic arthropods.

CULTIVATION OF SPIROCHAETES.

Another important step in our knowledge concerning spirochaetes is that they can be cultivated in vitro. All efforts to cultivate them under ordinary conditions, suitable for the great majority of bacteria, have given negative results in the hands of many bacteriologists all over the world. Levaditi (1906), it is true, succeeded in cultivating *S. gallinarum* and *S. duttoni* in collodion sacks placed, according to the usual technique, in the peritoneal cavity of rabbits. Under these conditions the spirochaetes multiplied and lived for 73 days or more. Successful cultivation in vitro has, however, only been recently accomplished by Noguchi (August, 1912), by adding a few drops of citrated rat or mouse blood, containing the spirochaetes, to sterile ascitic or hydrocele fluid (10 to 15 cc.) in tubes containing pieces of freshly excised rabbit's kidney. Precautions against bacterial contamination are imperative; it is best to collect the infected blood at the 48th to the 72d hour of the disease, and the tubes should be maintained at 36° C. He experimented with *S. duttoni* and two strains of *S. recurrentis* which he calls *kochi* and *obermeieri*. *S. duttoni* was still virulent after the ninth transplantation; *S. kochi* was transplanted 29 times, subcultures being made every four to nine days, the maximum growth being attained about the ninth day. This strain appeared to lose its virulence by prolonged culture. *S. obermeieri* attained its maximum growth on the seventh day, and was still virulent after having attained the seventh subculture.

To sum up, then, we have represented in the blood-inhabiting spirochaetes of warm blooded animals a group of microorganisms which, under natural conditions, are mainly conveyed by blood-sucking ectoparasites within which they undergo a process of development and in which they are hereditarily transmitted. Spirochaetes are not specialized parasites. Infection may take place through the skin or mucous membrane to which the spirochaetes gain access by being deposited thereon in the arthropod's dejecta or by the infested individual scratching or rubbing himself with hands which have become contaminated with the contents of the vermin which they have crushed. The lesions produced by the bites of the arthropods and the excoriations inflicted upon the individual by himself greatly facilitate the entrance of the spirochaetes.

FURTHER STUDIES ON THE RÔLE OF THE HYPOPHYSIS IN THE METABOLISM OF CARBOHYDRATES.

THE AUTONOMIC CONTROL OF THE PITUITARY GLAND.*

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(From the Laboratory of Surgical Research of the Harvard Medical School.)[1]

SYNOPSIS.

1. Introductory.
2. Hypophysial versus bulbar (Bernard) punctures.
3. Experiences with stimulation of superior cervical ganglion.
   a. After division of the sympathetic cords in the neck.
   b. After division of both sympathetic cords and vagi.
   c. After division of the splanchnic nerves.
   d. After spinal cord transection at T. IV segment.
   e. After spinal cord transection and division of both vago-sympathetic trunks.
   f. After administration of nicotine (Langley).
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5. Bernard piqûres after spinal cord transection.
6. Summary.
7. Conclusions.

Appendix. The significance of "available glycogen."
Glycosuria following spinal cord transection.

1. Introductory.

In a former paper from the Hunterian Laboratory in Baltimore[2] it was stated that: *In view of the ease with which hyperglycæmia may be produced by hypophysial lesions it is possible that our views in regard to the glycosurias of supposedly encephalic origin need some revision.* The present communication deals with certain studies pursued in this direction.

It had been observed that a transient glycosuria and polyuria were of common occurrence after a canine hypophysectomy, whereas after the same operative procedure, provided it stopped short of the manipulation of the hypophysial stalk necessary for a total removal, sugar was rarely, if ever, present. The presumption, therefore, was a natural one, in view of the glycogenolysis which follows the administration of glandular extracts, that the manipulation had led to a discharge of secretion. In this connection, moreover, it was assumed that the glycosurias and polyurias which not uncommonly follow fractures of the cranial base were possibly due to a contusion of the pituitary body itself, rather than to an excitation of some one of the various predicated glycosuric or diuretic centers.

2. Experiences with Bernard and Hypophysial Piqûres.

Some inquiry among physiologists who, for one purpose or another, had employed a Bernard piqûre in their investigations, showed that there was considerable disagreement as to the most effective site for the puncture, and in one preserved specimen it was seen that the needle had been introduced above the tentorium, and the end of its track lay suspiciously near the infundibulum. Hence, in the spring of 1911, some tentative studies of this matter were made by W. E. Dandy and Henry Fitzsimmons in the Hunterian Laboratory.

As in Bernard's original studies,[3] the observations were made on rabbits. Under primary anæsthesia (ether in amounts insufficient to cause glycosuria) a sterile copper wire of measured length was introduced to the proper depth through a primary cranial perforation. The wire was left *in situ*, so that the track could subsequently be identified. The method was controlled by making certain lateral punctures, which showed that the mere insertion and subsequent carrying of the wire would cause no symptoms of irritation or discomfort.

Our object was to compare the effect of a Bernard piqûre of the supposed sugar center in the fourth ventricle with one which entered the pituitary fossa itself. After some anatomical studies, it was found, for the purpose of an hypophysial piqûre, that the wire could be introduced from a median frontal position and passed along the ethmoidal groove to the sella turcica.

Not all of the experiments were successful—for reasons which at the time were not apparent ("available glycogen," etc.). Some fairly typical Bernard punctures failed to give glycosuria, and one typical hypophysial puncture gave a negative result: also a number of atypical (lateral or too short) Bernard piqûres gave actual glycosuria, and one merely an extreme diuresis. However, two or three of these preliminary observations may be recorded, for the sake of the chronology of our story.

The following is an example of a fairly *typical puncture of the Bernard type* producing glycosuria:

No. XVI. ***June 23, 1911.*** **Male rabbit. A pre-operative catheter specimen of urine gave no reduction of Fehling's solution.**

10.30 a. m. Through a median cranial perforation just caudal to the tentorium the wire was passed for a distance of 1.6 cm. towards the floor of the fourth ventricle and cut off extracranially. Prompt recovery. At 3 p. m. 3 cc. of urine obtained by catheter gave marked reduction of Fehling's solution.

June 24, a. m. **Urine obtained on catheterization continued to give a reduction of Fehling's solution.**

June 25, a. m. **A catheter specimen showed absence of reducing substance.**

June 26. **Urine gave no reduction by Fehling's solution. Animal sacrificed at 9.30 a. m.**

The *post mortem examination* revealed a median piqûre, the

* Presented at the meeting of the American Physiological Society, Cleveland, December 30, 1912.

[1] These studies were for the most part made during the past year or two in the Hunterian Laboratory of the Johns Hopkins University.

[2] Goetsch, Cushing and Jacobson: Carbohydrate tolerance and the posterior lobe of the hypophysis cerebri. Bull. Johns Hopkins Hosp., 1911, xxii, 165-190.

[3] Claude Bernard: Leçons de physiol. exper. (Cours de semestre d'hiver.) Paris, 1855. Also: Leçons sur le physiologie et la pathologie du système nerveux. Paris, 1858.

wire passing slightly backward from the exact perpendicular to the surface of the skull. The wire had penetrated the mid-cerebellum; it had entered the brain stem to an unnecessary depth, extending half way through the pons. Its position in the fourth ventricle was slightly cephalic to Bernard's point. There was practically no evidence of traumatic extravasation along the course of the wire and no inflammatory reaction.

The following is an example of a successful *hypophysiat puncture* producing glycosuria:

No. XVIII. *June 28, 1911.* Female rabbit. Urine before operation showed no reduction of Fehling's solution. At 11.30 a. m., through an anterior cranial perforation a wire was passed into the sella, with presumable accuracy. The slight external bleeding was easily checked. At 5 p. m. a specimen of urine obtained by catheter reduced Fehling's solution.

June 29. At 9 a. m. the urine gave no reduction of Fehling's solution. Animal sacrificed. At *autopsy* the wire was found to pass directly backward into the pituitary fossa. The gland was much ecchymosed. There was practically no extravasation along the track of the wire.

We had begun to have some inkling of a possible control by the so-called sugar center of Bernard over the discharge of a substance from the gland capable of glycogenolysis, and a few experiments were made with this in mind. The following is an example of the *double punctures* (a primary Bernard and secondary hypophysial, or the reverse) which were performed:

No. XIV. *June 21, 1911.* Male rabbit. Urine by catheter before operation showed no reducing body by Fehling's test. At 11 a. m. both cervical sympathetics were cut, with characteristic vaso-dilatation of ear vessels, narrowing of the pupils, etc. At 12 m. a Bernard piqûre was made, without complications. A catheter specimen obtained a few moments before the puncture showed no reducing body. At 2.05 p. m. the urine gave a marked reduction of Fehling's solution.

June 22, a. m. Urine voided during night proved negative for reducing bodies by Fehling's solution. Rabbit in good condition.

June 23. Urine gave no reduction of Fehling's solution.

June 24. Morning urine showed continued absence of reducing substance. At 10.45 a. m. *hypophysial puncture* performed under primary ether. At 12 m. urine obtained by catheter showed abundance of sugar.

June 25. Collected urine gave no reduction.

June 26. Urine obtained by catheter gave no reduction of Fehling's solution. Animal sacrificed at 9.35 a. m.

On *post mortem examination* the Bernard piqûre was found to pass through the cerebellum at the proper angle, the tip of the wire having barely reached the floor of the fourth ventricle. In the case of the hypophysial piqûre the wire had impinged on the floor of the sella turcica. There was evidence of some extravasation along the path of this second wire and also in the pituitary body itself, but there were no apparent ecchymoses in the tuber cinereum.

As our subsequent experiences have taught us, an experiment of this type would only have been conclusive had the spinal cord as well as the cervical sympathetics been divided before the punctures, and time allowed for the reaccumulation of glycogen. Under these conditions, as will subsequently be shown, the Bernard piqûre should not, and the hypophysial piqûre should, have given glycosuria. These early experiments, therefore, merely served to show that an hypophysial puncture would discharge glycogen as readily as would a typical Bernard piqûre.

If the contention of our predecessors, that the pars nervosa of the hypophysis plays an important rôle in the carbohydrate mechanism of the body, were to prove correct, it seemed not unlikely that a medullary piqûre of the Bernard type would serve to discharge the secretion of the posterior lobe in the same manner that such an impulse is believed to liberate the active principle of the adrenals.

Some studies (unpublished) by W. E. Dandy demonstrated the presence of non-medullated fibers coursing from the carotid plexus into both lobes of the pituitary body. These fibers accompany the vessels which he and Goetsch described[4] as constituting the essential circulation of the organ. This histological demonstration of a sympathetic nerve supply to the gland spoke in favor of a possible nervous influence over its secretion. It had been suggested, moreover, that the inevitable glycosuria which occurred in a series of rabbits used for testing hæmodynamic responses for cerebrospinal fluid might have been due to the trauma and excitation of the cervical sympathetic trunk during the exposure of the carotid artery for attachment to the kymographion, rather than to the presence in the fluid itself of posterior lobe secretion.

3. Effect of Stimulating the Superior Cervical Sympathetic Ganglion.

With these possibilities in mind, some preliminary tests were carried out to ascertain if the assumption of a nervous control over the pituitary body would endure. It was found (first in the case of the rabbit) that when the cervical sympathetic cord[5] was traumatized by repeated manipulations there was no subsequent occurrence of glycosuria. When, however, the dissection of the cervical sympathetic was carried higher in the neck, namely, to the superior cervical ganglion, sugar in large amounts promptly appeared in the urine. The record of a typical experiment showing this phenomenon follows:

Protocol I. *Faradic stimulation*[6] *of right superior cervical ganglion: resultant glycosuria.*

July 26, 1911. Large adult female cat. 1.30 p. m. Administration of ether begun. Urine obtained by catheter showed absence

[4] Dandy and Goetsch: The blood supply of the pituitary body. Am. Jour. Anat., 1910-11, xi, 137.

[5] It may be well to recall the anatomical variations of the cervical sympathetic trunk in the three species of laboratory animals used in the experiments. In the neck of the *dog* and *cat* the vagus and sympathetic cord lie in the same sheath. As one traces this vago-sympathetic trunk upward in the *cat*, the sympathetic fibers leave the vagus anteriorly, to expand into the superior cervical ganglion, which lies just anterior to the lower ganglion of the vagus. In the *dog* the vagal ganglion and the superior cervical ganglion exist in close association, with, however, a line of cleavage clearly visible between them. On dissection the two ganglia are found to be connected only by a rather heavy bundle of fibers. The cervical sympathetic trunk in the *rabbit* is entirely separated from the vagus: in some of the animals, moreover, the sympathetic fibers run in two separate bundles on both sides of the neck. The superior cervical ganglion is connected with the ganglion of the vagus by a delicate fiber strand.

[6] It may be noted here that in all of these experiments the method of bipolar stimulation was used, with a current which could be borne on the tongue.

of sugar by Fehling's and Nylander"s tests. The superior cervical ganglion was exposed and isolated by gauze dissection. Bipolar faradic stimulation of ganglion by weak, moderate, and fairly strong currents at intervals for twelve minutes. Marked pupillary dilatation occurred during stimulation.

2 p. m. Etherization ended. Urine obtained by catheter gives marked reduction of Fehling's and Nylander's solutions. On fermentation sugar was found to be present in amounts of over 1 per cent. Reading on polarization; dextro, 1.8 per cent.

This basic experiment showing that *stimulation of the superior cervical ganglion causes a prompt and outspoken glycosuria* we have found to hold true in forty observations on the cat, rabbit and dog, the one requisite for the glycosuria being the presence of what we will fully describe later on as "available glycogen." Needless to say, the amount of ether required for anæsthetization, as shown by control experiments, has been far from sufficient to account for the glycogenolysis.

Cats and rabbits have been used for the most part, on account of the ease with which the ganglion may be exposed in these animals; but the essential phenomenon has been confirmed sufficiently often on dogs to show that the same response occurs in this species. It may be said, however, that the glycosurias of the dog have proved to be less prompt in occurrence and of a lower sugar percentage than those of the cat and rabbit. This may perhaps be explained on the ground that the same strength of stimulus was employed in all cases, and it may not have been of sufficient intensity to occasion an equal glycosuria in the larger animal. The results, moreover, may have been somewhat modified by the fact that specimens of canine urine were not obtained until the animals voided; whereas in female cats and in both male and female rabbits catheterization was resorted to.

In the preceding protocol the glycosuria would naturally be attributed to the faradic excitation. It has been demonstrated, however, in subsequent experiments on cats and rabbits that other forms of stimulus suffice to cause the prompt appearance of sugar in the urine. The following is one of many experiences which show that the mere manipulation of the superior cervical ganglion essential to the free dissection of the structure may provoke glycosuria:

Protocol IX. *Mechanical stimulation of vagus and sympathetic trunk: no glycosuria. Subsequent exposure of the right superior cervical ganglion: prompt glycosuria.*

August 4, 1911. Large female rabbit. 3.45 p. m. Urine obtained by catheter gave no reduction of Fehling's solution. Under local anæsthesia the right vagus was exposed and mechanically stimulated many times, the sympathetic trunk meanwhile being walled off by rubber protective.

4.20 p. m. Urine obtained by catheter (30 minutes after the traumatic stimulation of the vagus) negative for sugar by Fehling's solution.

4.25 p. m. The right sympathetic trunk was subjected to a repeated mechanical stimulus in like fashion, and thirty minutes later (4.55 p. m.) a catheterized specimen of urine showed no sugar.

5 p. m. The superior cervical ganglion was freely exposed by carrying the dissection higher in the neck, and thirty minutes later (*viz.* 5.43 p. m.) the urine, obtained by catheterization, gave marked reduction of Fehling's solution.

August 5. 9 a. m. Urine (catheter specimen of 15 cc.) gave no reduction of Fehling's solution. Repetition of stimulation of the superior cervical ganglion failed to evoke a second melliturla.

The preceding record indicates that the mere exposure by dissection of the superior cervical ganglion may elicit a marked glycosuria, whereas intentional traumatic manipulation of the pre-axial sympathetic fibers, as well as of the vagus, may not suffice to produce this effect.

On ascertaining that stimulation of the superior cervical ganglion in dogs, cats and rabbits caused a marked glycogenolysis, the problem of the finer relationship of the fibers in the sympathetic trunk to this phenomenon naturally called for investigation.

The cervical sympathetic system originates in pre-ganglionic fibers which emerge in the ventral roots from the lowest cervical to the third thoracic spinal segment. These pre-ganglionic fibers for the most part course through the inferior to the superior cervical ganglion. From the latter structure the pathway is continued onward by post-ganglionic fibers, the nerve cells with their essential synapses lying in the ganglion.

With such a conception of the cervical sympathetic system, it seemed unlikely that the glycosuria from stimulation of the ganglion could have been due to an excitation of nerve fibers passing in the direction of the inferior ganglion, whence they might enter the spinal cord or continue to the abdominal viscera.

(a) *After Section of the Pre-ganglionic Fibers.*—As exemplified in the foregoing protocol, traumatization of the sympathetic cord in the neck of a rabbit failed to produce a glycosuria, and in subsequent more carefully executed experiments even faradic stimulation was found to be equally ineffectual. With the belief that the impulses controlling the superior cervical ganglion must ascend in this cord, we carried out a series of experiments on rabbits, in which, after sectioning the cervical sympathetic (a procedure which in itself does not result in glycosuria), the lower proximal end of the divided nerve was stimulated by the faradic current. Ascertaining that this excitation caused no melliturla, the upper cephalic end of the divided sympathetic nerve was stimulated in like manner. As no sugar appeared in the urine after this second procedure, faradic excitation was supplied to the superior cervical ganglion, with a resultant prompt glycosuria. The data of such an experiment follow:

Protocol XLVIII. *Faradic stimulation (peripheral and central) of divided pre-ganglionic cord: no glycosuria. Stimulation of homolateral superior ganglion: prompt glycosuria.*

May 1, 1912. Small adult male rabbit. 11 a. m. A catheter specimen of urine negative for sugar by Fehling's and Nylander's tests.

11.15 a. m. Section of right sympathetic cord in neck. Faradic stimulation (coil at 6 cm.) of lower proximal end of divided right sympathetic trunk for three intervals of 30 seconds each, with intermissions of the same period.

2 p. m. Catheter specimen (17 cc.) of urine: negative for sugar (Fehling and Nylander).

2.10 p. m. Similar stimulation of upper distal end of divided right sympathetic cord.

4.20 p. m. On catheterization 15 cc. of urine obtained: negative Fehling's and Nylander's tests.

4.30 p. m. Exposure of right superior cervical ganglion.

4.38. Faradic stimulation (coil at 6 cm.) of right superior cervical ganglion for three intervals of 30 seconds, as above.

4.45 p. m. Closure of wound.

5.10 p. m. Urine on catheterization, 10 cc., with a marked reduction of Fehling's and Nylander's solutions.

May 2. Animal in normal condition. 9 a. m. Urine (catheter specimen) negative for sugar (Fehling and Nylander).

Believing that possibly the fibers in the distal (cephalic) trunk might have lost their excitability during the interval of three hours between the first and second excitations, the procedure recorded above was modified as follows. The sympathetic cord on one side was sectioned and its lower proximal end stimulated. Then, after allowing sufficient time for a possible reducing body to appear in the urine, the sympathetic cord on the opposite side was divided and its upper distal extremity immediately stimulated. In this way the possibility of loss of excitability in the cords from exposure was eliminated, but the procedure failed to give mellituria until the superior cervical ganglion was stimulated. The protocol of such an experiment follows:

PROTOCOL LVI. *Faradic stimulation (central left, and peripheral right) of divided pre-ganglionic cords: no glycosuria. Stimulation of right ganglion: eventual glycosuria.*

May 13, 1912. Adult female rabbit. 10 a. m. Catheter specimen of 4 cc. negative by Fehling's and Nylander's tests.

10.05 a. m. Section of left sympathetic trunk in middle of neck.

10.07 a. m. Faradic stimulation (coil at 6 cm.) of lower proximal end of divided left sympathetic trunk for three intervals of 30 seconds each, with intermissions of the same period.

10.13. Closure completed.

12.55 p. m. By catheter, 16 cc. of urine, giving no reduction of Fehling's or of Nylander's solution.

1 p. m. Section of right sympathetic trunk in middle of neck.

1.05 p. m. Corresponding faradic stimulation (coil at 6 cm.) of upper distal end of divided right sympathetic trunk.

1.14 p. m. Closure completed.

3.35 p. m. Urine by catheter (18 cc.) negative for sugar (Fehling's and Nylander's).

3.45 p. m. Exposure of right superior cervical ganglion begun.

3.50 p. m. Faradic stimulation (coil at 6 cm.) of right superior cervical ganglion for three intervals with intermissions of 30 seconds each.

4 p. m. Closure completed.

5 p. m. Catheterization unsuccessful.

May 14, 10 a. m. Catheterization unsuccessful.

4.30 p. m. Clear specimen of urine obtained by catheter: marked reduction of Fehling's and Nylander's solutions.

The following conclusions may be drawn from these two typical protocols: (1) That faradic stimulation applied to the cervical sympathetic cord is ineffectual as an agent for producing mellituria, and (2) that excitation of the superior cervical ganglion gives a positive result and causes sugar to appear in the urine even when both sympathetic cords are divided in the neck.

Two possible explanations of this failure to elicit glycosuria by stimulation of the pre-ganglionic cord are as follows: The first and more probable is that degenerative changes in the non-medullated fibers occur with such rapidity at the points of contact with the electrodes that they cease to conduct an adequate stimulus. A less probable explanation is that heretofore undescribed pre-ganglionic fibers, stimulation of which leads to glycosuria, leave the spinal cord high in the cervical region and make some direct connection with the superior cervical ganglion.

(b) *After Division of the Vago-Sympathetic Trunk.*—In so far as the positive results from stimulating the ganglion itself are concerned, the question arises, does the excitation applied to the ganglion affect centripetal fibers leading to some glycogenolytic center, or are we dealing with the efferent side of a reflex which exhibits its end result by the presence of sugar in the urine? If the former, it might be conceived that the impulse travels to the cerebrospinal axis cephalad along the internal carotid artery or along one of the cervical nerves, or even downward along the vagus or sympathetic trunk to enter the cord at a lower level.

The foregoing protocol speaks against the view that the impulse travels downward along the sympathetic trunk; for in these experiments on rabbits excitation of the ganglion gave rise to glycosuria even with a divided cervical sympathetic cord. In the cat, moreover, the sympathetic cord runs in the same perineurilemma with the vagus, and stimulation of the superior cervical ganglion in this animal is effective even after section of this combined vago-sympathetic trunk. Such an experiment follows:

PROTOCOL VII. *Preliminary section of vago-sympathetic trunk: stimulation of superior cervical ganglion: subsequent glycosuria.*

August 4, 1911. Small male cat. 2.18 p. m. Etherization begun.

2.24 p. m. Exposure of vago-sympathetic trunk: urine then obtained by abdominal pressure negative for sugar by Fehling's solution.

2.29 p. m. Right vago-sympathetic trunk sectioned in middle of neck.

2.44 p. m. Right superior cervical ganglion exposed by dissection. Etherization ended.

3.14 p. m. Urine gave marked reduction of Fehling's solution.

4.30 p. m. Urine gave positive reduction of Fehling's solution.

August 5, 9.50 a. m. Urine negative for sugar by Fehling's solution.

In subsequent experiments it was found that stimulation of the superior cervical ganglion invariably provoked glycosuria after both vagi and the two sympathetic trunks in the neck had been sectioned. It was ascertained also that stimulation of the ganglion after it had been freed from all its connections except the distal cephalic trunk along the internal carotid artery likewise caused glycosuria. This was demonstrated in many experiments on the dog, cat and rabbit; but inasmuch as the mere exposure of the structure by dissection may cause glycogenolysis, the observations were not conclusive, for sufficient excitation might already have passed from the ganglion along some other connections to give rise to the hyperglycæmia and subsequent glycosuria.

(c) *After Division of the Splanchnic Nerves.*—Having excluded the possibility of an impulse passing downward from the ganglion, our next step was to eliminate the chance that a centripetal impulse passed to the cord or to the brain stem.

Assuming that these glycosurias are due to the discharge of hepatic glycogen through neurogenic impulses, it was believed that a reflex through the central nervous system could be excluded either by section of all nerves to the liver or by division of the spinal cord cephalad to the superior limit of the origin of the splanchnic nerves, the relation of which to the glycosurias of hepatic and adrenal origin Macleod[1] has so well shown.

Thus we first endeavored to eliminate this possibility of some unknown nervous connection between the superior cervical ganglion and the liver by preliminary division of all the autonomic fibers in the gastro-hepatic ligaments. The results served merely to corroborate, in the cat, Macleod's observations made on the dog. As no animals survived in whom the urine became sugar free we were unable to test the effect of a subsequent stimulation of the superior cervical ganglion.

(d) *After Transection of the Spinal Cord.*—It became necessary therefore to resort to the second possible method of excluding a splanchnic course of the impulse—namely, the complete transverse section of the spinal cord above the splanchnic nerves.

To our surprise, this procedure almost invariably gave rise to a glycosuria in the animals used (dog, cat and rabbit). Fortunately, however, these glycosurias from spinal transection as a rule proved to be of short duration, the urine of the animals soon becoming sugar free. It was found, moreover, that if food was withheld after section of the cord above the splanchnics (*i. e.*, on a level with the fourth pair of thoracic nerves), neither stimulation of the superior cervical ganglion nor of the splanchnic fibers in the gastro-hepatic ligament, nor a second division of the cord, would elicit glycosuria. This as we found in the course of time, is due to the fact that, in response to the primary stimulus, all the available glycogen of the body has been discharged in the form of dextrose; for by the judicious feeding of these animals a second mellituria of extreme degree may be caused by any of the stimuli which prove effective in the normal animal.

The details of a typical experiment illustrating this reaccumulation and redischarge of glycogen are given below:

Protocol XXVIII. *Preliminary spinal cord transection with glycosuria: reaccumulation of glycogen: secondary glycosuria following stimulation of superior cervical ganglion after division of vago-sympathetic cord.*

For four days previous to beginning the experiment the animal, a large female cat, was confined and abundantly fed. At no time did the urine show sugar.

December 19, 1911, 9.45 a. m. Etherization begun.

10 a. m. Urine on catheterization negative for sugar by Fehling's solution.

10.15 a. m. Laminectomy performed: complete transverse division of spinal cord at fourth thoracic segment.

10.30 a. m. Operation completed. Urine by catheter gave marked reduction of Fehling's solution.

5.45 p. m. On catheterization, urine still showed strong reducing qualities to Fehling's solution.

December 20, 8.30 a. m. Animal in good condition. On catheterization 50 cc. of urine obtained: negative for sugar by Fehling's solution.

9 a. m. Animal given by stomach tube 100 cc. of milk, warmed to body temperature, containing 20 grams of saccharose.

12.45 p. m. Urine by catheter gave slight reduction of Fehling's solution.

2.40 p. m. Animal given 100 cc. of warm milk containing 5 grams of saccharose.

December 21, 8.30 a. m. Urine by catheter gave slight reduction of Fehling's solution.

12.45 p. m. Urine by catheter negative for sugar by Fehling's and Nylander's tests.

1.30 p. m. Etherization begun.

1.45 p. m. Section of right vago-sympathetic cord in neck before exposure of right superior cervical ganglion. Faradic stimulation (coil at 8 cm.) of ganglion intermittently for fifteen minutes (ten stimulations of ten seconds each).

2 p. m. Etherization ended.

2.15 p. m. Urine on catheterization gave marked reduction of Fehling's and Nylander's solution.

5 p. m. A few drops of urine, obtained by catheter, gave marked reduction of Fehling's solution.

December 22, 10.30 a. m. Urine by catheter (50 cc.): no reduction of Fehling's solution.

2.30 p. m. Urine on catheterization (15 cc.) gave no reduction of Fehling's or Nylander's solution. Animal died under the anæsthetic given preparatory to second stimulation of the superior cervical ganglion.

At *autopsy* the complete division of the spinal cord at the fourth thoracic level and complete section of the right vago-sympathetic trunk were verified.

As a control experiment, to demonstrate that an identical stimulus applied to the superior cervical ganglion is ineffective in causing the reappearance of glucose in the urine, provided the animal be not permitted to reaccumulate glycogen by feeding, the following is included:

Protocol XXIX. *Preliminary cord transection, with glycosuria: subsequent stimulation of superior cervical ganglion, without glycosuria, as no available glycogen.*

Previous to beginning the experiment the animal, a female cat, was confined and well fed for two days. At no time was there glycosuria.

December 20, 1911, 11 a. m. Etherization begun.

11.15. Urine on catheterization negative for sugar by Fehling's test.

12 m. Laminectomy, with complete transverse section of spinal cord at fourth thoracic level.

12.15 p. m. Catheterization unsuccessful.

2.45 p. m. Urine obtained by catheter strongly reduced Fehling's solution.

5 p. m. Catheterization unsuccessful.

December 21, 9 a. m. Urine by catheter (50 cc.) caused no reduction of Fehling's solution.

9.45 a. m. Etherization begun.

10 a. m. Vago-sympathetic trunk divided in middle of neck. Dissection of superior cervical ganglion. Faradic stimulation (coil at 8 cm.) applied to ganglion intermittently for fifteen minutes. Ether stopped at 10.15.

10.30 a. m. Catheterization yielded 10 cc. of urine, negative for sugar by Fehling's solution.

5 p. m. Catheterization unsuccessful.

December 22, 9.45 a. m. Under ether anæsthesia the abdominal wall was opened in the mid-ventral line. Bladder aspirated and emptied: 50 cc. of urine obtained; negative for sugar by Fehling's

[1] Macleod. Amer. Jour. Physiol., 1908, xxii, 373: Macleod and Ruh. *Ibid*, 397: Macleod and Pierce. *Ibid*, 1911, xxviii, 403; 1912, xxix, 419.

solution. Hepatic nerves in gastro-hepatic ligament dissected out and sectioned. Faradic stimulation (coil at 8 cm.) applied to ligament on hepatic side of area of section.

10.40 a. m. Abdominal wound closed.

2 p. m. Animal sacrificed.

At autopsy the section of the spinal cord at the level of the fourth thoracic nerves was verified. Urine in bladder (5 cc.) gave no reduction of Fehling's solution.

A comparison of the protocols of these two animals, which were subjected to identical conditions, leads one to the conclusion that the feeding resorted to in the first animal made possible the second mellituria from excitation of the superior cervical ganglion. In the second animal, after failure to elicit glycosuria from the ganglion stimulation, the several procedures about the gastro-hepatic ligament (any one of which would be certain in a glycogen-containing animal to evoke a tremendous glycosuria) were employed, demonstrating, by a sugar-free specimen of urine, that the animal had at the time no glycogen available for discharge.

The first of these two experiments is particularly significant, inasmuch as glycosuria was produced by excitation of the superior cervical ganglion after division not only of the homolateral vago-sympathetic trunk in the neck, but also of the spinal cord above the level of the splanchnic fibers. The only possible pathway for the impulse to travel, if we are dealing here with a purely nervous reflex to the liver, would be downward along the contralateral vagus. That the pathway is not caudalwards along the contralateral truncus sympathicus we have already shown.

(e) *After Spinal Cord Transection and Division of Both Vago-Sympathetic Trunks.*—It would seem that the likelihood of contralateral vagus conduction must be remote, for the vagus will probably be found to inhibit rather than induce glycogenolysis in the liver. However, to eliminate this possibility a cat's spinal cord was divided above the splanchnics, the animal was fed until it was believed that glycogen had reaccumulated, and then the vago-sympathetic cords were sectioned on both sides of the neck. Subsequent stimulation of the superior cervical ganglion gave rise to a very marked glycosuria.

PROTOCOL XXXIII. *Preliminary spinal cord transection, with glycosuria: reaccumulation of glycogen. Stimulation of superior cervical ganglion, with glycosuria after division of both vago-sympathetic trunks.*

Previous to the beginning of the experiment the animal, a full-grown cat, was fed in its cage on a very liberal diet. All specimens of urine were sugar free.

March 25, 1912, 2.15 p. m. Etherization begun.

2.30 p. m. *Laminectomy* with division of spinal cord at the fourth thoracic segment.

2.40 p. m. Operation completed. Urine by catheter reduced Fehling's solution very strongly.

5 p. m. Urine by catheter gave marked reduction of Fehling's.

March 26, 10.45 a. m. Urine by catheter (30 cc.) negative for sugar by Fehling's and Nylander's tests.

11.15 a. m. Animal given by stomach tube 100 cc. of milk, at 37° C., containing a small amount of saccharose.

2 p. m. Urine by catheter gave no reduction of Fehling's solution.

2.15 p. m. Animal given by stomach tube 100 cc. of milk at 37° C., containing a small amount of saccharose.

5 p. m. Urine gave no reduction of Fehling's solution.

5.10 p. m. Etherization begun.

5.15 p. m. Section of left vago-sympathetic trunk in middle of neck.

5.18 p. m. Section of right vago-sympathetic trunk in middle of neck.

5.25 p. m. Exposure of right superior cervical ganglion.

5.28 p. m. Faradic stimulation (coil at 8 cm.) of right superior cervical ganglion for 30 seconds.

5.32 p. m. Similar stimulation for 30 seconds.

5.33 p. m. Etherization ended: closure begun.

5.38 p. m. Closure completed.

5.48 p. m. Urine obtained by catheterization gave extreme reduction of Fehling's and Nylander's solutions.

March 27, 10 a. m. Urine by catheter (18 cc.) gave a marked reduction by Fehling's and Nylander's solutions. Gravimetric determination showed 2 per cent monosaccharide content.

11 a. m. Animal sacrificed.

At *autopsy* the complete division of the spinal cord at the level of the fourth thoracic nerves and the two vago-sympathetic cords was verified.

Such an experiment—but one of a series of confirmatory observations—conclusively demonstrates that in the glycosurias resultant from stimulation of the superior cervical ganglion we are dealing not with a nervous reflex, but with a chemical stimulus to glycogenolysis arising somewhere in the cephalic course of the cervical sympathetic fibers. Observations similar to the one just quoted have been made on many cats and rabbits with uniformly positive results.

Though a corresponding experiment has not been made on the dog, nevertheless the glycosurias which occur in this species after section of the spinal cord, as well as after stimulation of the superior cervical ganglion, lead to the presumption that in these animals likewise the cervical sympathetic system is concerned in sugar metabolism in a way heretofore unappreciated, completely independent of a reflex arc which connects with its final relay in the splanchnic fibers.

In this group of experiments, as should be observed, all the nerves leading to any of the thoracic or abdominal viscera were divided before the final stimulus was applied to the superior cervical ganglion—that is, with the exception of the phrenic nerve; but it is inconceivable that we are dealing with a glycogenolysis excited by impulses which travel along this nerve.

(f) *With Open Synapses After Administration of Nicotine.*—Still further proof of the chemical nature of the impulse liberated ultimately by stimulation of the superior cervical ganglion is furnished by experiments with nicotinized animals in which the drug was given intravenously in amounts sufficient to open with certainty the synapses of the sympathetic system. Langley[8] has made use of 5 cc. of a 1 per cent solution of nicotine, given in this manner, to break the synaptic connections, but for absolute surety we have used larger amounts for dogs and proportionately larger amounts for cats.

[8] Langley and Dickinson: Proc. Roy. Soc., 1889, xlvi, 423. Also: The action of various poisons upon nerve fibers. Jour. Physiol., 1890, xi, 509. Also: Pituri and Nicotin: *Ibid,* 265.

The administration of nicotine intravenously calls for the maintenance of artificial respiration, for almost immediately after injection of the drug there ensues a hyperpnœa and polypnœa of extreme degree, followed in a few seconds by total apnœa necessitating artificial respiration.

Our purpose in applying Langley's method was to assure ourselves that any glycosuria evoked by excitation of the superior cervical ganglion was the result of glycogenolysis inaugurated by the liberation of a chemical body and not of a neurogenic glycogenolysis through some unknown reflex arc somewhere in the organism. Hence, in these nicotinized animals, very soon after the presumed separation of the synapses the spinal cord was divided at a level with the fourth thoracic nerves. This procedure should elicit a prompt glycosuria if the stimulus need traverse no synapse to reach its final point of activity. In every case this procedure failed to cause a glycosuria.

Following this demonstration that section of the spinal cord is an ineffectual glycogenolytic stimulus in a nicotinized animal, stimulation of the superior cervical ganglion was resorted to, and this was quickly followed by an outpouring of large amounts of sugar into the urine—a definite argument in favor of the view that the stimulus from the superior cervical ganglion is independent of any essential synapse and leads to the discharge of a chemical substance producing glycogenolysis.

The experiment was first carried out on the cat, and it was found that after the preliminary tracheotomy under ether, the injection of the nicotine in itself maintained a complete anæsthesia.[9] In three successive experiments the results corresponded—no glycosuria from spinal cord section, glycosuria from stimulation of the superior cervical ganglion. The same procedure applied to a dog was followed by identical reactions. The data of this experiment follow:

PROTOCOL LXXIV. *Spinal cord transection in a nicotinized animal: no glycosuria. Stimulation of superior cervical ganglion: prompt glycosuria.*

Previous to the experiment the animal, an adult male dog, had been kept in a cage for fourteen days. By stimulation of the sciatic nerve glycosuria had been produced nine days previously. For eight days before the experiment the urine on daily tests was sugar free. The animal was in good condition and was affected in no appreciable way by the previous stimulation.

August 21, 1912. Urine under cage (170 cc.) negative for sugar by Fehling's and Nylander's solutions. Specific gravity, 1032.

10.32 a. m. Etherization begun. Tracheal tube inserted and right external jugular vein exposed. Complete evacuation of bladder.

10.45 a. m. Injection of 8 cc. of 1 per cent solution of nicotine (Merck) was made into the right jugular vein. Artificial respiration (bellows) was commenced, and was maintained until the end of the experiment. Administration of ether stopped just before the nicotine solution was administered.

11 a. m. Laminectomy and complete transection of the spinal cord at the level of the fourth thoracic nerves.

1.15 p. m. Evacuation of bladder by abdominal pressure: urine (18 cc.) negative for sugar by Fehling's and Nylander's tests.

1.20 p. m. Exposure of right superior cervical ganglion. Faradic stimulation (coil at 8 cm.) was applied to the ganglion for three intervals of thirty seconds each, with intermissions of the same period.

3.50 p. m. Urine (22 cc.) obtained by abdominal pressure gave marked reduction of Fehling's and Nylander's solutions. Nicotine was still effective in opening synapses, as proved by failure to evoke pupillary dilatation on stimulation of the cervical sympathetic cord on the left side. Animal sacrificed.

These results appear to present definite proof that the melliturias with which we have been dealing are not of neurogenic character throughout. That the nicotine was given in sufficient amount in these experiments was evidenced by the failure in all cases to elicit glycosuria by spinal cord transection and by the fact that at the conclusion of the experiments stimulation of the sympathetic trunk in the neck resulted in no pupillary dilatation—both phenomena being dependent on the integrity of the synapses. The impulse, then, aroused by stimulation of the superior cervical ganglion must necessarily have been such that it passed through no synapses before discharging the store of glycogen or liberating the chemical messenger which caused the glycogenolysis. The latter alternative is, of course, by far the more likely.

(g) *After Extirpation of the Posterior Lobe of the Hypophysis.*—Proof that a chemical substance plays the essential rôle in the melliturias following stimulation of the superior cervical ganglion would of course be obtained if some organ capable of giving rise to such a substance were to be excised and subsequent ganglionic stimulation fail to produce glycosuria. We have found that glycosuria does not appear after the customary ganglionic stimulation in dogs in whom the pars nervosa of the hypophysis has previously been removed. We have used four dogs for this test, and in all of them we have failed to elicit the customary glycogenolytic response to the excitations. A typical protocol follows:

PROTOCOL XLVII. *Stimulation of the superior cervical ganglion after extirpation of the posterior lobe of the hypophysis: no glycosuria.*

The posterior lobe of the hypophysis having been removed from an adult male dog eight weeks previously (*i. e.* February 15: Jacobson's series, No. 12), the animal was fed bountifully for a week before stimulation, and for the three antecedent days, in order to assure the presence of available glycogen, an aqueous sugar solution was given by stomach tube (saccharose, grams 40) twice daily. At no time did sugar appear in the urine.

April 25, 1912. Urine obtained just previous to operation possessed no reducing bodies (Fehling's and Nylander's solutions).

11 a. m. Etherization begun.

11.20 a. m. Exposure of superior cervical ganglion on the left side. Faradic stimulation (coil at 6 cm.) applied to ganglion for three intervals of thirty seconds each with intermissions of the same period.

11.30 a. m. Closure completed.

5 p. m. No urine under cage.

April 26, 9 a. m. No urine under cage.

[9] As originally devised, the experiment was attempted on animals to which, instead of ether, chloretone was given in alcoholic solution as an anæsthetic. We were unable to elicit glycosuria in these animals by any available method—even by the administration of large intravenous doses of adrenalin.

5 p. m. No spontaneous micturition, so animal given a whiff of ether, and 250 cc. of urine obtained by abdominal pressure. No reduction of Fehling's and Nylander's solutions. Specific gravity 1.050.

April 27, 9 a. m. Urine under cage, 105 cc. Specific gravity 1.042. Negative for sugar.

The uniformity of the results in other experiments of this type gives further support to the view that stimulation of the superior cervical ganglion causes a discharge into the blood stream of the posterior lobe secretion.[10] Whatever may be the nature of the chemical substance thus discharged, it is presumably carried through the vascular system to the glycogen storehouses of the body, either in the liver or in the muscles, where it inaugurates glycogenolysis. The exact method by which this liberation of glycogen as dextrose into the circulation is brought about is conjectural: the hypophysial substance may act as the necessary hormone; it may stimulate nerve terminals to liberate glycogenase; it may activate the glycogenase.

4. Effects of Direct Stimulation of the Hypophysis.

We had long been aware that certain manipulations of the gland during the performance of a canine hypophysectomy would evoke glycosuria, and the hypophysial piqûres mentioned in this paper were supposed to occasion a similar mechanical discharge of the secretion. Having shown that a discharge of the active principle, as evidenced by a succeeding glycosuria, would follow the electrical stimulation of a superior cervical ganglion when severed from all connections except its post-ganglionic fibers, we were led, as a next step, to faradize the gland itself.

Our observations in this direction have been made both upon the cat and dog, in which animals the hypophysis may be easily exposed by a transphenoidal route through the mouth. Female cats were preferred, as they were more susceptible to catheterization. Ether was given, but in an amount insufficient to cause a complicating glycosuria from the drug. The animals were catheterized immediately after the onset of surgical anæsthesia, and after the hypophysis was exposed a second sample of urine was taken, as a precaution against the possibility of the operative trauma evoking glycosuria. In none of these animals was sugar found in the urine in either specimen. After a faradic stimulation was applied to the hypophysis, however, a marked glycosuria in most cases promptly occurred. The record of a typical experiment follows:

PROTOCOL LXXVII. *Direct faradic stimulation of the hypophysis, with prolonged glycosuria.*

December 25, 1911. Female cat. 10.05 a. m. Etherization begun. Urine (10 cc.) negative for sugar by Fehling's and Nylander's reactions.

10.07-10.50 a. m. Exposure of hypophysis by buccal route.

10.53 a. m. Urine (5 cc.) negative for sugar by Fehling's and Nylander's tests.

10.54 a. m. Faradic stimulation of gland for two minutes. Ether removed. Prompt recovery.

12.10 p. m. Urine (10 cc.) strongly reduces Fehling's and Nylander's solutions.

December 26, 9 a. m. Urine voided during night (55 cc.) showed abundant sugar (Fehling and Nylander).

December 27, 9 a. m. Urine (20 cc.) negative for sugar (Fehling and Nylander).

December 28 and 29. Urine remained negative for sugar by all tests.

This experiment indicates that direct faradic stimulation of the hypophysis is capable of causing a marked glycosuria, prompt in appearance and enduring for some hours. That this glycosuria cannot be attributed to the mere operative trauma incidental to the transphenoidal approach is well shown by the following experiment, in which, owing to surgical difficulties, an incomplete denudation of the gland was made at the first operation, no glycosuria resulting even after faradic stimulation of the neighborhood. At a subsequent operative session the gland was fully exposed and glycosuria promptly followed the stimulation. This was repeated on five successive occasions, a sufficient interval for the reaccumulation of glycogen being allowed between the stimulations.

PROTOCOL LXXIX. *Incomplete denudation of hypophysis with faradization: no glycosuria. Subsequent complete exposure, with faradization and glycosuria, repeated on five occasions, with intervals for glycogen reaccumulation.*

January 10, 1912, 10.10 a. m. Female cat anæsthetized.

10.13 a. m. Catheter specimen of urine (10 cc.) negative for sugar by Fehling's and Nylander's tests.

10.15 a. m. Small transphenoidal opening in base of sella with incomplete exposure of gland: difficult operation.

10.53 a. m. Catheter specimen (11 cc.) negative (Fehling and Nylander).

10.54 a. m. Faradic stimulation with electrodes at bottom of sphenoidal wound for two minutes.

1 p. m. Catheter specimen (8 cc.) negative for sugar (Fehling and Nylander).

January 11, 12 and 13. Urine voided on each of these days remained sugar free.

January 14, 9 a. m. Urine voided (30 cc.) negative for sugar (Fehling and Nylander).

10.20 a. m. Ether anæsthesia. With a more complete removal of bone from the sellar base the hypophysis was fully exposed.

11.05 a. m. Urine by catheter (8 cc.) negative for sugar (Fehling and Nylander).

11.08 a. m. Faradic stimulation of gland for three minutes.

January 15, 9 a. m. Urine obtained since stimulation (15 cc.) showed abundant sugar by Fehling's and Nylander's tests.

January 16 to 21 inc. Urine voided on each of these days negative for sugar (Fehling and Nylander).

January 22. Morning urine (15 cc.) negative for sugar by Fehling's and Nylander's solutions.

[10] It should be noted that after any operative removal of the pars nervosa some of the pars intermedia may still remain in contact with the ventricular stump of the hypophysial stalk, along which the nerves course to the gland. Under these circumstances it might be assumed that the stimulus applied to the superior cervical ganglion could still serve to discharge sufficient hyaline substance to evoke glycosuria. Hence, in this group of experiments, even had a slight glycosuria occurred after the ganglion stimulation, our conclusions need not have been modified. As it was, the absence of glycosuria in these animals, in view of their having been well fed and confined to cages for at least a month before the ganglion stimulation, is the more striking, and offers additional, though negative, proof that stimulation of the superior cervical ganglion results in a glycosuria having its chemical origin in the hypophysis.

Under ether anæsthesia the hypophysis was again exposed and faradic stimulation applied to the gland for three minutes; duration of anæsthesia twenty minutes. Urine (4 cc.) obtained by catheter just before stimulation negative for sugar (Fehling and Nylander).

Urine (7 cc.) by catheter fifteen minutes after stimulation showed abundant sugar by Fehling's and Nylander's solutions.

January 23, 9 a. m. Urine voided since operation (25 cc.) showed abundant sugar by Fehling's and Nylander's tests: gravimetrically, 5 per cent sugar.

January 24 to February 6 inc. Animal fed on routine laboratory diet for these two weeks. Urine remained sugar free.

February 7. Fourth exposure and stimulation of hypophysis. Urine (18 cc.) obtained by catheter at the beginning of ether anæsthesia, and also (4 cc.) just before the stimulation was begun, negative (Fehling and Nylander) for sugar. Faradic stimulation applied to the gland for three minutes. Duration of ether anæsthesia, twenty minutes. Urine voided during the following night (25 cc.) showed abundant reduction of Fehling's and Nylander's solutions.

February 8 to 12 inc. Urine remained sugar free on these days, the animal being fed on routine laboratory diet.

February 13. Fifth exposure and faradic stimulation (three minutes) of hypophysis, followed by a marked glycosuria.

February 14 to March 6 inc. Urine remained sugar free.

March 7. Sixth exposure and faradic stimulation of hypophysis, as on the previous occasion. A prompt glycosuria of 4 per cent sugar content in urine followed.

The foregoing protocol clearly indicates that direct faradic stimulation of the pituitary body, with an intact nervous system, will incite mellituria. This, as well as our preceding experiences, had begun to make us reasonably certain that the gland, and probably the pars nervosa, under the proper stimulus liberates a chemical substance capable of inducing glycogenolysis. Others have expressed the view that there exists a "diabetic center" in the tuber cinereum, and that this, rather than the pituitary body, accounts for the glycosurias which our predecessors observed in the earlier experiments reported from the Hunterian Laboratory. Hence, to make the foregoing experiment still more conclusive, it was necessary to eliminate, by a spinal cord transection, the possibility that our stimulus might have acted on some center in the cerebrospinal axis capable of eliciting a purely neurogenic mellituria.

It was found that glycosuria may be evoked by direct stimulation of the gland substance even after division of the spinal cord above the splanchnic outflow, provided opportunity be allowed for the reaccumulation of glycogen necessarily discharged by this procedure (*cf.* appendix). In this series of experiments it was not considered necessary to section the vagi and the sympathetic trunks in the neck, as our earlier observations on the melliturias inaugurated by stimulation of the superior cervical ganglion showed that impulses capable of eliciting glycogenolysis did not descend by way of these nerves. The record of one of these experiments will suffice.

PROTOCOL LXXII. *Preliminary transphenoidal exposure of hypophysis, with glycosuria. Transection of spinal cord, with glycosuria. Reaccumulation of glycogen. Direct stimulation of hypophysis with resultant glycosuria.*

August 1, 1912. Adult female cat. 11.20 a. m. Etherization begun.

11.25 a. m. Catheterization: 16 cc. of sugar free urine obtained.

11.30 a. m. Exposure of hypophysis by buccal route begun.

11.40 a. m. Operation completed: a quick, uncomplicated procedure, giving a good view of both lobes of the gland. Urine by catheter (8 cc.) negative for sugar by Fehling's test.

11.45 a. m. Faradic stimulation (coil at 6 cm.) of hypophysis; for three intervals of thirty seconds each, with intermissions of the same period.

11.55 a. m. Closure of soft palate completed.

August 2, 9 a. m. No urine voided. A specimen obtained by abdominal pressure (50 cc.) caused marked reduction of Fehling's solution. Gravimetrically, 2.5 per cent sugar.

August 3, 9 a. m. Urine under cage (65 cc.) caused no reduction of Fehling's solution.

August 4 to 9 inc. Urine sugar free. Routine feeding in cage.

August 10, 9 a. m. Urine under cage (50 cc.) caused no reduction of Fehling's or Nylander's solution.

10 a. m. Etherization started. Laminectomy and transection of spinal cord at fourth thoracic segment. Wound closure completed at 10.30.

August 11, 10 a. m. Bladder emptied by abdominal pressure. Urine (45 cc.) reduced Fehling's and Nylander's solutions. Animal then given 50 cc. of warmed milk by stomach tube.

August 12, 9 a. m. Urine by abdominal pressure (48 cc.) negative for reducing bodies by Fehling's and Nylander's solutions. Given 50 cc. of warmed milk by stomach tube.

3.30 p. m. Urine by abdominal pressure (18 cc.) negative for sugar. Given 50 cc. of warmed milk, containing 2 grams of saccharose, by stomach tube.

August 13, 9 a. m. Urine by abdominal pressure (52 cc.) gave no reduction of Fehling's or Nylander's solution. Given 50 cc. of warmed milk, containing 3 grams of dextrose.

2.30 p. m. Urine by abdominal pressure (12 cc.) negative for sugar.

2.45 p. m. Re-exposure of hypophysis through original pathway. Faradic stimulation of the gland (coil at 8 cm.) for two intervals of forty-five seconds each with an intermission of thirty seconds. After stimulation the posterior lobe of the gland, with a small portion of the anterior lobe, was excised.

3.15 p. m. Etherization ended. Reclosure of palate completed.

August 15, 9 a. m. Urine obtained by abdominal pressure (34 cc.) showed a marked reduction of Fehling's and Nylander's solutions. Animal in good condition. Given 50 cc. of milk at 37° C.

5 p. m. Urine by abdominal pressure (16 cc.) still reduced Fehling's and Nylander's solutions. Animal given 50 cc. of milk at 37° C.

On August 16 the urine became sugar free and remained so. The animal was given milk by stomach tube for four days—a sufficient time for the reaccumulation of glycogen—and an attempt was then made to stimulate the superior cervical ganglion, with the expectation that, as in other experiments of the kind, no mellituria would be evoked, owing to the posterior lobe extirpation of August 13. The animal died under the anæsthetic soon after the exposure of the ganglion.

At autopsy the complete transverse division of the spinal cord and the opening into the sella turcica, with extirpation of the posterior lobe, were verified.

The foregoing record indicates that direct stimulation of the hypophysis evokes glycogenolysis and glycosuria through a chemical messenger rather than by any nervous mechanism connecting the encephalon with the abdominal viscera.[11]

[11] As will be observed, we have employed, as the basis of these experiments, the discharge or otherwise from the gland of the substance capable of producing glycogenolysis. The gland doubtless contains other substances or hormones, or else this same substance is capable of eliciting other reactions—notably those of a hæmodynamic nature.

In a single experiment we endeavored to obtain the record of a hæmodynamic response to direct glandular faradization, but no change in carotid pressure occurred during the interval of stimulation. This matter calls for further investigation; for it seems not unlikely that a considerable period of time must elapse before the secretion of the pars nervosa enters the circulation, particularly if, as we believe to be the case, it reaches the blood stream through the intermediation of the cerebrospinal fluid. Under these circumstances no hæmodynamic evidence of hypophysial discharge need be expected in a carotid tracing until some minutes after the initial stimulus, and the same is true of the glycogenolytic hormone, for this substance doubtless likewise takes the same route to the blood stream.

We are in need of chemical reactions to detect small quantities of these substances in the blood, such as Folin has given us for adrenalin; but it will first be necessary to determine the chemical composition of the active principle and possibly to synthetize it before satisfactory test reactions can be expected.

5. Bulbar Piqûres After Spinal Cord Transection.

As during the progress of these studies our premise of a nervous impulse passing from the bulb by way of the cervical sympathetic and presiding over the secretory activity of the posterior lobe of the pituitary body received further support, many collateral experiments were made, which need not be detailed here, as they do not add essentially to the strength of the argument.

There is but one further step which may deserve mention; and this brings us back to the original piqûre of Bernard in the rabbit which heretofore has been thought to provoke hepatic glycogenolysis solely through an autonomic mechanism involving splanchnic nerves and adrenal glands.

It seemed reasonable to expect that a typical bulbar piqûre in a nicotinized animal would fail to produce glycosuria, owing to the opened synapses throughout the autonomic system; whereas stimulation of the pituitary body itself should not fail to give sugar even in an animal under the full influence of this drug. Furthermore, in view of our experiences with spinal cord transection and reaccumulation of glycogen, the possibility of producing glycosuria by a bulbar piqûre through the intermediation of the hypophysis, after such a transection above the splanchnics, naturally suggested itself.

The nicotine experiments in the rabbit were unsuccessful, as the animals invariably succumbed to such a dosage as we thought necessary to insure opening of the synapses. Hence the negative bulbar piqûre under these circumstances remains a matter of presumption. Positive results, however, were obtained by piqûres in the animals after spinal cord transection.

Observations were made on four normal rabbits. After the spinal transection at the fourth thoracic level, they were allowed to feed, in preparation for the subsequent medullary piqûre, until it was believed that glycogen had reaccumulated. The piqûres were made through the cerebellum into the rhombencephalon, after the method of Dandy and Fitzsimmons. Three of the animals were subjected to identical experimental conditions: in two of them the piqûre evoked a marked glycosuria. The data of one of the experiments follow:

PROTOCOL XLVIII. *Transection of spinal cord at T. IV: subsequent Bernard piqûre, with glycosuria.*

April 22, 1912. Adult male rabbit. 11 a. m. Urine obtained by catheter: no reduction of Fehling's or Nylander's solution.

12 m. Laminectomy: spinal cord sectioned at the fourth thoracic level. Wound closed at 12.30. Prompt recovery, with resumption of feeding.

4 p. m. Urine obtained by catheter (30 cc.) reduced Fehling's and Nylander's solutions. Animal given raw apple.

April 23, 9 a. m. In good condition. Urine on catheterization (115 cc.) negative for sugar by Fehling's and Nylander's solutions.

10.50 a. m. Trephine opening for medullary piqûre.

11 a. m. Piqûre wire inserted in usual manner.

12 m. Urine by catheter (23 cc.) strongly reduced Fehling's and Nylander's solutions. Gravimetrically, 1.25 per cent of monosaccharide; by polarization, dextro 1.2 per cent.

1.45 p. m. Urine obtained by catheter (20 cc.) caused marked reduction of Fehling's and Nylander's solutions. Gravimetrically 4 per cent sugar.

4 p. m. Animal sacrificed. Urine in bladder (16 cc.) caused marked reduction of Fehling's and Nylander's solutions. Section of spinal cord found to be complete at the level of fourth thoracic nerves. Typical bulbar piqûre.

Such an observation indicates that the impulse from a Bernard medullary piqûre, in addition to its well-known effect on the adrenals, serves to discharge a glycogenolytic substance from some other gland of internal secretion—obviously in this case the pituitary body. To be sure, the vagus and sympathetic trunks had not been divided, but our earlier experiments have excluded the possibility of the vagus playing a functional rôle in these cervical glycosurias.

In the third of the three experiments carried out under identical surgical circumstances the Bernard piqûre failed to evoke a glycosuria. However, on subsequent stimulation of the superior cervical ganglion sugar promptly appeared in the urine, showing that there was available glycogen, and justifying the conclusion, in view of the two other experiments, that the piqûre had been faulty.

We used the fourth rabbit of this series to tell whether the medullary piqûre would cause glycosuria if performed after section of the two sympathetic trunks in the neck in addition to the cord transection; for a positive result would indicate that some impulse could reach the gland other than by way of the known cervical pre-ganglionic fibers. The piqûre actually gave glycosuria; but no definite conclusions are permissible, owing to the finding at autopsy of an additional fiber bundle—not a part of the vagus—which lay in the carotid sheath and which had not been sectioned; this in all probability was a detached filament of the cervical sympathetic cord. We have had no opportunity to repeat the procedure, and merely record the observation here as being suggestive.[12]

[12] It is of interest to recall the early views of Bernard and Eckhard in regard to the emergence of splanchnic fibers in the three upper thoracic nerves. Eckhard in particular (Die Stellung der Nerven beim künstlichen Diabetes. Beitr. z. Anat. u. Physiol., 1869, iv, 3-32) supported the conception that the typical bulbar piqûre elicited glycosuria by splanchnic excitation, the specific glycogenolytic fibers supposedly leaving the upper cord. It would seem that these earlier observers erred in assuming a downward

Though the experiments in this particular group are few, with the evidence in hand we feel justified in stating that a medullary piqûre, after division of the spinal cord above the level of the splanchnics, will cause glycosuria, evidently by the discharge of some chemical substance which evokes glycogenolysis; and that the hypophysis furnishes this substance seems by far the most likely explanation.

From the results of the experiments which have been cited in this paper it is fair to assume the existence of a nervous control on the part of the sympathetic system over one form at least of the secretory activities of the pituitary body. The particular function of the gland—and presumably of its posterior lobe—on which our studies have been based concerns the elaboration and discharge of a substance capable of evoking glycogenolysis.

Doubtless other of the so-called ductless glands operate under a similar autonomic influence, and in the case of the adrenal this has been particularly well brought out by Macleod and his collaborators. However, owing to the comparative ease with which the post-ganglionic fibers which reach the pituitary gland may be experimentally isolated from the rest of the nervous system, this member of the ductless gland series would seem to offer a better opportunity for the demonstration of a clearly chemical glycosuria occasioned by the discharge of an internal secretion than does even the adrenal.

It remains to be shown, in the first place, just how the functional[18] or pathological glycosurias originating from disorders of the hypophysis actually occur, whether from some unusual and continued neurogenic influence, from an external chemical stimulus, or from an actual increase, through glandular hyperplasia, of the normal secretory output: in the second place, how the glandular secretion actually serves to evoke the glycogenolysis, whether it acts on nerve endings in the hepatic and muscular storehouses of glycogen, or whether it liberates and transforms glycogen by a direct chemical interaction within the cell.

However these things may be, certainly in the future the discharge of a chemical messenger from the hypophysis will have to be taken into account when considering the encephalic glycosurias, whether of purely emotional or of pathological origin. It may be noted in closing, moreover, that heretofore the relation of the glands of internal secretion to the sympathetic system proper, alone, has been made the particular object of study. Doubtless in time their equally important relation to the craniosacral system will be investigated and studies made to determine the impulses which inhibit secretion.

course for the fibers which leave the cerebrospinal axis in the first three thoracic nerves. The glycosurias which they obtained were undoubtedly of the same origin as those with which this paper deals. The later work of Langley has definitely limited the superior origin of the splanchnic nerves to the fifth and very rarely to the fourth thoracic nerves. Hence the impulse aroused in the first three thoracic nerves must travel upward in order to elicit the ensuing glycosuria, and not downward as in the splanchnic collection.

[18] It has been suggested that the glycosurias of adolescence, as well as those of pregnancy and other physiological states, are largely influenced by coincident hypophysial changes. (The Pituitary Body and Its Disorders. 1912. J. B. Lippincott Company).

6. Summary.

Provided there is a storage of glycogen available for discharge:

1. A piqûre of the hypophysis in the rabbit is comparable, in its glycosuric response, to a piqûre of Bernard's so-called sugar center in the fourth ventricle.
2. Stimulation of the superior cervical ganglion, by faradization or even by the manipulations necessary for its exposure, causes glycosuria in the rabbit, cat and dog.
3. Stimulation of the superior cervical ganglion after exclusion of all possible downward impulses to the abdominal viscera by way of the vagi, cervical sympathetic trunks, or spinal cord, leads to glycosuria.
4. Stimulation of the superior cervical ganglion after separation of all synapses of the sympathetic system by administration of nicotine, causes glycosuria.
5. Direct faradic stimulation of the hypophysis itself, after exposure by a transphenoidal operation, gives glycosuria even after preliminary transection of the spinal cord and cervical sympathetic trunks.
6. If the posterior lobe of the hypophysis has previously been removed by operation the usual stimulation of the superior cervical ganglion fails to give glycosuria.
7. Direct faradic stimulation of the hypophysis provokes glycosuria even after transection of the spinal cord above the splanchnics.
8. A Bernard piqûre will likewise cause glycosuria even after transection of the spinal cord above the splanchnics.

7. Conclusions.

The pituitary body, and more particularly its posterior lobe, plays a significant rôle in the metabolism of carbohydrates, and its action in this respect is under the control of fibers which reach the gland by way of the superior cervical sympathetic ganglion. Stimulation of this nervous pathway at the so-called sugar center in the fourth ventricle, at the superior cervical ganglion, and by excitation of the pituitary body itself, liberates a chemical substance which causes glycogenolysis and glycosuria, independent of any possible nervous impulse reaching the glycogen-holding cells of the muscles or abdominal viscera.

Appendix.

The Significance of Available Glycogen.

Throughout the foregoing pages frequent use has been made of the term "*available glycogen*" when explaining the occurrence or otherwise of glycosuria in an animal subjected to a given stimulus. We feel the necessity of explaining at some length our position in regard to the glycogen content of the body, in view of the importance of the subject in all experimental studies of glycosuria.

Bernard, in his original description of the glycosuria incited

by a medullary puncture, found that sugar did not appear in the urine of animals which had been previously deprived of food. Naturally, under these circumstances, the starvation led to a decrease in the carbohydrate content of the liver. The store of glycogen may be exhausted under other conditions —in strychnine poisoning, for example; for if the drug is given in amounts sufficient to cause convulsions not enough glycogen remains to be discharged by the ordinary methods of eliciting glycosuria.

An essential factor in our experiments was the production, by a second excitation, of another wave of hyperglycæmia and glycosuria after the animal's urine had become sugar free. It was observed that the initial period of glycosuria, after one or another of the potent stimuli—for example, after spinal cord transection—was surprisingly short, showing either that the effect of the excitation was transient or else that the stimulus discharged but little of the glycogen held by the body. Moreover, some histological studies were made of the glycogen content of the liver cells after staining with Best's carmine, and it was seen that there was an abundant glycogen residual in many of the cells even after a copious glycosuria had followed an antecedent stimulus.

Hence we anticipated that a further discharge of glycogen could be brought about by the repetition of some known form of glycogenolytic excitation after the animal's urine had again become sugar free; but it was found that a second stimulus would rarely, if ever, evoke glycosuria unless the animal in the interval had been fed in such a manner as to encourage a further storage of glycogen .

A few of our experiences in this regard have been related in connection with some of the foregoing protocols, but it was largely the negative results which finally brought us to our present interpretation of the matter—namely, that there exists in the body a supply of glycogen in considerable amount shortly after feeding, but which diminishes rather rapidly. This supply of course does not include all of the glycogen of the body, not even the total glycogen content of the liver, but corresponds with what we have come to designate as "available glycogen."

The distinguishing features of this store of glycogen are, the readiness with which it may be discharged by the stimuli which we have used (Bernard piqûre, hypophysial piqûre, stimulation of the superior cervical ganglion, cord division, section of the nerves to the liver, and direct stimulation of the hypophysis) and its failure to reaccumulate unless feeding be resorted to.

Our evidence in no way justifies the belief that, after application of one or another of the glycogenolytic stimuli, all of the glycogen of the body is exhausted—a phenomenon which may possibly occur after prolonged starvation or severe strychnine poisoning. Indeed we feel assured that this is not the case; for there seems to exist, in addition to the basic store of glycogen, a more unstable supply capable of being liberated or mobilized by a degree of stimulation which fails to influence the basic supply. In all likelihood the long continued application of our weaker excitations might ultimately have resulted in the liberation of the basic or immobile glycogen, but of this we have no proof. We have therefore interpreted our results from the standpoint of this rather vague classification of the glycogen content of the body—the basic or difficult of discharge, and the mobile or available supply.

The question immediately arises as to whether animals always have an available glycogen content if their tissue carbohydrates have in no way been previously discharged. In the case of dogs we have found that stimulation of the superior cervical ganglion by a mild faradic current always results in glycosuria, provided the animal has been bountifully fed and has been confined in a cage for three of four days previous to the procedure: under these circumstances in no instance have we failed to elicit glycosuria. On the other hand, the application of the same excitation under similar conditions in the case of dogs which have been taken from the animal yard just before the observation seldom results in glycosuria. Such a phenomenon seems to indicate that the activities of the dog in the yard constantly form a demand upon the glycogen supply of the body, with the result that the weak excitation which we have used is ineffective when the more unstable transient "available glycogen" is thus exhausted.

The constancy with which glycosuria has followed excitation of the superior cervical ganglion in dogs confined to their cages for periods of over three days we feel is a very important factor in the argument that such a stimulation affects the pars nervosa of the hypophysis; for in every instance the animals in whom the posterior lobe had been extirpated failed to show glycosuria, though they had previously been in confinement and though practically all of them had a high sugar tolerance, assuring a plentiful glycogen supply.

Evidence favorable to this conception of glycogen storage is afforded by such an observation as the following. Stimulation of the superior cervical ganglion of a dog that had been allowed the freedom of the paddock failed to evoke glycosuria. The animal was then confined to his cage for some days on the same routine diet, when the ganglion on the opposite side was exposed and stimulated, with a resultant copious discharge of sugar—owing, we presumed, to the storage, betweenwhiles, of glycogen available for discharge.

Under the usual laboratory conditions the cat and rabbit apparently possess a more easily available store of glycogen than does the dog. These animals not only lead a quiet laboratory existence, but the diet also constitutes an important factor in the provision of an adequate content of mobile glycogen. For the cats, milk has been given, while the abundant carbohydrates in the vegetables fed to the rabbits assure large amounts of glycogen in these animals. Hence it does not seem at all strange that we should have found our weak stimuli effective in practically all cases in cats and rabbits, whereas with dogs the same excitations at times proved ineffective unless special care had been taken to insure inactivity and abundant feeding.

For these reasons, in our varied experiments failure to obtain glycosuria has been considered from the standpoint of available glycogen. If any procedure failed to provoke glyco-

suria, the subsequent demonstration of the presence or absence of mobilizable glycogen was considered necessary; and no result was considered reliable unless this check was made. The three procedures which we have employed for this purpose are (1) stimulation of the superior cervical ganglion; (2) division of the spinal cord, and (3) stimulation of the hepatic nerves in the gastro-hepatic ligament.

As our investigations chiefly concerned the relation of the superior cervical ganglion to the hypophysis, the negative results of ganglionic stimulation concerned us most. But in no case were we able to elicit glycosuria by either of the other two methods after a primary excitation of the ganglion had proved ineffective. The three procedures appear to be equally capable of causing a discharge of glycogen; and stimulation at any one of the three situations apparently results in the discharge of all available glycogen, if available glycogen be present.

Spinal Cord Transection and Glycosuria.

In the course of these studies, in order to assure ourselves that the stimulation of the cervical sympathetic ganglion did not reach the abdominal viscera and act upon the adrenals or splanchnic system by the operation of some retrograde or "antidromic" (Bayliss) impulses which operated contrary to the Bell-Magendie law, we attempted to exclude this possibility by the preliminary transection of the spinal cord above the splanchnics. As might possibly have been expected, this procedure invariably provoked glycosuria provided there was available glycogen. As we are unfamiliar with any similar observations, the matter may deserve a word of comment.

It was found in the dog, cat or rabbit that the transection of the cord at any segment provoked glycosuria, though most of the divisions were made cephalad to the level of emergence of the splanchnics. The operation is simple and brief, and in our routine procedure, after the laminectomy a grooved director was passed beneath the cord and its enveloping meninges. A complete transverse section was assured by cutting down upon the director, and bleeding from the stumps was controlled, if necessary, by the application of small bits of raw muscle.

In dogs and cats ether was used, but in the case of rabbits local anæsthesia by infiltration methods, with cold water or cold salt solution, sufficed. Control observations were made, to eliminate the possibility that the glycosuria might be due to the anæsthetic. Cocaine was not employed as the local anæsthetic, on account of the likelihood of occasioning a glycosuria by sensitizing the terminals of the sympathetic fibers to the action of adrenalin.

One striking feature of the glycosuria provoked by spinal cord section is the promptness with which sugar makes its appearance. In many of our experiments catheterization was resorted to as soon as the operative wound was closed; and in many cases the glycosuria was demonstrable within ten minutes after the transection.

Another characteristic of these glycosurias is their short duration, for as a rule the urine becomes sugar free by the end of the first twenty-four hours, unless the sugar content of the food has exceeded the temporarily lowered carbohydrate assimilation limit or unless some further glycogenolytic stimulus has been superadded.

In the case of the rabbit no difficulty has been experienced in the question of feeding if it has been essential to the problem at hand to assure the reaccumulation of glycogen in order to test the effects of a subsequent stimulus; for these animals will usually resume their nibbling of the food placed before them immediately after the cord transection. In the few animals which have failed to do so, attempts to administer food artificially have been futile. After transection in the cat we have found it desirable to administer the milk by stomach tube, as indicated in the protocols which have been given.

By far the greater number of our cord transections have been made at the fourth thoracic segment, for at this level the division can be made caudad to the emergence of fibers into the cervical sympathetic cord and cephalad to the splanchnic outpouring. However, our few experiments with transection at other segments indicate that cord division at any level provokes mellituria provided the animal has a store of available glycogen.

In all likelihood the transection stimulates all the tracts in the cord, more especially the fibers going to the splanchnic nerves, and causes hepatic glycogenolysis through activation or liberation of glycogenase, as Macleod has shown. There is doubtless an increased outpouring of the active principle of the adrenals into the blood stream, and the response may be entirely in accord with the view that a Bernard medullary piqûre acts by adrenal stimulation. However, in view of the rôle played by the cervical sympathetic in the control of the pars nervosa, it seems not unlikely that spinal transection acts by sending forth a general excitation to all the glands of internal secretion, whose secretory discharge results in mellituria.

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INDUCED PNEUMOTHORAX IN THE TREATMENT OF PULMONARY DISEASE.*

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Rest has long been accepted as an important condition for the recovery of inflamed tissues. In many locations pain necessitates it and physicians exaggerate and prolong the remedial measure that nature suggests. Particularly in tuberculous infections has its enforcement given brilliant results, and numerous observations have led to the conclusion that rest is as valuable a remedy in pulmonary tuberculosis as in tuberculosis of other regions. Towards the end of the last century the frequent beneficial effects of pleural effusion upon tuberculous lesions in the lung arrested attention. The relation is often striking. Concomitantly with the appearance of fluid, fever abates, cough and sputum decrease, and the patient's general condition improves. Aspiration of the exudate may be followed by a recurrence of the previous symptoms, which again subside as the fluid reaccumulates. L. Spengler has published striking instances of this not uncommon occurrence. He suggests injecting silver nitrate into the pleural cavity to increase and prolong the effusion. Galliard writes of such effusions under the title *pleurésies providentielles*. Mosheim has collected many convincing observations from the literature. Konselman has made it the subject of an interesting study. The beneficial results are ascribed to the immobilization of the diseased lung.

One of the most dreaded complications of advancing tuberculosis of the lungs is the occurrence of pneumothorax. Coming as a rule at the end of a prolonged and wasting illness it usually marks the rapid approach of death. West, in 101 cases, found that in 75 per cent death occurred within fourteen days of the onset of pneumothorax. Drasche, in 198 cases, found a rate of 71 per cent. Brunicke, Grissole, Valleix, and others regarded pneumothorax developing in the course of pulmonary tuberculosis as invariably fatal. Ruhle had never heard of a case ending in recovery with concomitant healing of the pulmonary lesion. Such instances, however, began shortly after to be recorded. At first isolated examples were published as medical curiosities, later the observations became more common. Of Drasche's 198 cases only one recovered completely. West reported 11 cured out of 167 instances. Mosheim considered that the tuberculous nature of some of West's cases was doubtful, and in a number of others the healing incomplete. He allowed only six definite recoveries; three without the appearance of pleural exudate, three with serous or sero-purulent exudate. In one of the six the pulmonary tuberculosis healed concomitantly. Mosheim reported one recovery in 42 instances of pneumothorax occurring in pulmonary tuberculosis. A number of the cases showed marked immediate improvement. Rose observed three recoveries in nineteen instances. Only eight of Spengler's twenty cases died; seven were discharged unimproved; one case recovered and the pulmonary lesion healed, but a serous exudate remained; four cases completely recovered, and in three of these the pulmonary lesion likewise healed.

Pneumothorax in itself is a very benign condition. The rapidly widening experience with induced pneumothorax, as we shall later point out, attests this. In healthy individuals complete collapse of one lung may occasion but trifling symptoms and easily escape detection. We have observed two instances of spontaneous pneumothorax in otherwise healthy men associated only with slight dyspnea on exertion, and a transient stitch in the side. Bach, Goodhart, Hall, Jochman, Pepper, Sale, Weber, West and others report similar cases. The fatal effects of pneumothorax in pulmonary tuberculosis must then be ascribed to associated conditions. Usually it is but a terminal event in a patient worn by rapidly advancing disease, and already overshadowed by death; the almost constantly associated pleural infection adds an extensive area for septic absorption; and in many instances mechanical conditions at the point of rupture induce fatally high intrapleural pressure.

Occasionally, even in advanced tuberculosis, the advent of pneumothorax marks the beginning of improvement in the pulmonary condition. The symptoms of progressing disease abate, the patient's general condition improves, and the signs of pulmonary involvement diminish. Such an observation led Carson, in 1821, to propose inducing pneumothorax as a therapeutic measure. Adams, in 1887, published the notes of a case of pulmonary tuberculosis in which profuse hemoptysis was associated with a large pulmonary cavity. With the sudden onset of pneumothorax the bleeding at once stopped and improvement in the patient's condition began. He also suggested the advisability of inducing pneumothorax under certain circumstances, but neither Carson nor Adams put the suggestion into practice. In 1882 Forlanini reported a number of striking instances of improvement following the occurrence of a spontaneous pneumothorax, and advised inducing pneumothorax in appropriate cases of pulmonary tuberculosis. In 1892 he began to practice the method, and in 1894 presented his observations before the Eleventh International Medical Congress held at Rome. In 1895 he reported the cure of a

* Those further interested in this subject can secure a reprint with twenty complete case histories from Dr. Louis Hamman, 714 Park Avenue, Baltimore.

case of grave pulmonary tuberculosis following the prolonged maintenance of pulmonary collapse with nitrogen gas. Although Forlanini continued to use the treatment he published no further reports upon the subject until 1906, since when a number of valuable contributions have come from his clinic.

In 1898 Murphy, though uninformed of Forlanini's work, was led on by the same considerations to use the method. He presents the records of five patients with pulmonary tuberculosis treated by nitrogen inflation of the pleural cavity. All showed striking immediate benefit from the treatment but none, at the time the report was made, had been under observation long enough to allow any conclusions to be drawn about its ultimate value. During the same year Schell published a brief note of a single case in which severe hemoptysis was controlled by inducing pneumothorax. In 1899, Lemke, a pupil of Murphy, presented a preliminary report of 53 cases treated by the method, but owing to the unfortunate death of the author, a fuller account never appeared. Apparently therapeutic pneumothorax was then abandoned in this country, for there are no further reports of its use until the past year, when Lapham, Rothschild, and Robinson and Floyd again have called attention to the procedure.

In 1906 appeared the first article by Brauer upon induced pneumothorax, and since this date the literature on the subject has been enriched by notable contributions from Brauer and his students. He has done more than any other observer to work out the fundamental mechanical and physiological principles of pneumothorax, and has brought valuable clinical and pathological material to the study of the method.

Selection of Cases for Treatment.

The application of induced pneumothorax has not been restricted to any particular disease or type of case. It has been made use of chiefly in pulmonary tuberculosis, but Brauer, Schmidt, Wellman, and others have similarly treated patients with bronchiectasis and chronic non-tuberculous infections of the lungs. It is evident that one-sided lesions are the most favorable, but in the late stages of pulmonary tuberculosis it is difficult to find strictly unilateral cases. To what extent the opposite lung may be be involved, and the patient still be a suitable candidate for the treatment, is variously approximated by different observers. Forlanini is lenient in this regard, while Brauer selects his patients with more rigor. It is only reasonable to assume that if immobilization is beneficial, exaggerated activity is harmful. If rest is of value to the diseased lung, we must see to it that the other is not overburdened by the increased demands made upon it. However, it must be pointed out that though both lungs may be affected, the disease is seldom equally active upon the two sides and as the side with the most marked activity is the one usually chosen for the operation, the opposite lung is generally equal to withstanding the added work put upon it. Experience upholds this conclusion, and indeed many observers claim that the untreated side is favorably influenced through the diminished toxemia, and the improved general condition of the patient that often follow the treatment. Murphy, in his original article, proposed the method particularly for "apical or monolobar tuberculosis in the early stage as the pathological conditions are such that the compression of the lung can be accomplished and adhesions are not likely to be found. I do not consider," he adds, "that it is indicated or practical in advanced or chronic tuberculosis as the fibrous tissue deposited in the lung will not permit compression of the lung nor will the pleuritic adhesions allow of gas injection." In practice Murphy's suggestions have never been carried out. All available reports deal only with cases of advanced pulmonary tuberculosis subjected to the treatment. The method is still on trial, and the tendency has been to establish its value in instances of the disease that have been uninfluenced by the usual hygienic-dietetic measures. When even under unfavorable conditions such value becomes apparent, induced pneumothorax will be given a wider field of application, and we are convinced that the ultimate sphere of its usefulness will be principally in moderately advanced cases of the disease. At present it is impossible to represent statistically the results of the treatment. It is only by studying the results in numerous individual cases that one can form an estimate of its value. Our own experience has been gathered from unfavorable and desperate cases of pulmonary tuberculosis. Many of the patients we operated upon at first were not selected in any medical sense. They were accepted because, conscious of their progressing disease, they were willing to risk a new method of treatment, while more suitable patients withheld their consent. Recently we have induced pneumothorax under more favorable conditions, and hope in the future to find the opportunity to test its value in earlier stages of the disease.

The Method of Inducing Pneumothorax.

There are two methods in use for inducing pneumothorax, the method advocated by Brauer, and the method originally used and still employed by Forlanini.

1. *Brauer's Method.*—He calls his method the Brauer-Murphy method, although the procedure recommended by Murphy is certainly much more like the operation of Forlanini. Murphy describes his operation thus: "A tenotomy puncture should be made through the derma; this allows the trocar to be easily inserted. The stilette in the trocar should be withdrawn when the rib is reached; the gas should now be turned on; the trocar should then be pushed inward, hugging the margin of the rib. When the parietal pleura is punctured the trocar advances rapidly and the gas begins to flow freely into the cavity unless adhesions exist. If adhesions be present the gas will not flow. The trocar should be taken out and inserted in the same manner in another position." Although Brauer's method is more complicated than Forlanini's, he warmly advocates it, claiming it is free from certain dangers which he believes the simpler method cannot safely avoid. About half an hour before the operation the patient receives a quarter grain of morphine. The location of the incision having been selected, the patient is arranged upon the table with this

area as the highest point. Unless there is some contraindication, the fifth or sixth intercostal space in the axillary area is chosen. Cushions are placed beneath the patient so that this portion of the chest will protrude and the ribs be held apart. Under cocaine anesthesia the skin, fascia and superficial muscles are divided by an incision five to seven centimeters in length. Through the incision the fascia of the intercostal muscles is divided and the fibres of the muscles separated with dull scissors or a small clamp. Through this opening the parietal pleura can be inspected, and its appearance indicates the presence or absence of adhesions. A dull cannula with an eye situated upon the side near its point is then thrust through the parietal pleura into the pleural space. The cannula is large enough to admit a small ureteral catheter and in certain cases Brauer uses a catheter to palpate the pleural cavity to determine the extent and density of pleural adhesions. If by appropriate observations it is evident that the cannula is in the pleural cavity and the pleural cavity is relatively free from adhesions, gas previously warmed to the body temperature is slowly allowed to run in. Brauer insists that at the first operation from 500 to 1000 cc. of gas should be introduced, since smaller amounts make the subsequent refillings less certain and more dangerous.

2. *Forlanini's Method.*—He, without anesthesia, introduces a small caliber aspirating needle connected with a suitable apparatus through the intercostal space, and thrusting it carefully forward ascertains when the point is in the pleural cavity by manometric readings. If the observation indicates that the needle is in the proper position the gas is then allowed to flow in. At the first operation Forlanini introduces only from 200 to 300 cc. of nitrogen, and gradually produces collapse by the further daily addition of small amounts until a complete pneumothorax has been produced.

After the first inflation the pneumothorax is enlarged and maintained by repeated injections of nitrogen. If the primary operation has been successful, physical examination, and particularly X-ray examination, indicate the position and extent of the pneumothorax and the secondary inflation can be carried out with safety and ease. For secondary inflations ordinary aspirating needles are employed in both methods.

As the object of the treatment is to maintain constant and, as nearly as possible, uniform collapse of the affected lung that gas is most desirable for injection which is least quickly absorbed. It has been found that nitrogen resists absorption from the pleural cavity longer than any other innocuous gas, and for this reason it is generally employed. Air may be used with equal success, but subsequent refillings must then be made more frequently.

Forlanini's method has decided advantages over the procedure advocated by Brauer. It is simpler, causes the patient very little pain, and therefore if local adhesions prevent the successful inflation of the pleural cavity at the first attempt, one may with good grace repeat the effort a number of times until finally perhaps a point is found where the pleural space is patent. Such an experience is by no means uncommon. It would be a formidable procedure to repeat the Brauer method five or six times. Brauer does not claim simplicity or ease for his method. He recognizes all the advantages that the Forlanini method has in this direction, but he urges that the latter operation is attended by grave danger, and therefore justly prefers to put himself and the patient to some inconvenience to avoid taking what he considers an unjustifiable risk.

The dangers attending induced pneumothorax are two, infection and air embolism. Infection of the pleural cavity may occur from without or through the lung. It is needless to emphasize the ease with which the pleural cavity may be infected, and superfluous to insist upon the importance of a rigid and irreproachable surgical technic in all the manipulations. With the necessary precaution, infection of the pleural cavity from without will rarely occur. However, v. Muralt, who is an able and efficient man, reports an instance. A patient operated upon by the Brauer method developed a stitch abscess and following this a rapidly fatal pyopneumothorax. One of our patients developed pyopneumothorax, possibly as the result of faulty technic. Infection of the pleural cavity through the lung may occur if the lung is injured by the needle during manipulation to find the pleural cavity, or by spontaneous rupture, or through a tear of the organ occasioned by the pull of adhesions when the pneumothorax is subjected to high pressure. Of these three possibilities we may say that we know of no instance in which the lung has been torn by adhesions, although Keller reports a case in which it is presumed to have happened. Knoblauch reports the development of local empyema in a patient operated upon by the Forlanini method. v. Muralt cites a case in which spontaneous rupture of the lung occurred during a secondary refilling. In advanced pulmonary tuberculosis such ruptures happen not infrequently, and perhaps this instance was not occasioned directly by the treatment.

More important than the danger of infection is that of air embolism. A few instances will illustrate its gravity. Lemke, in inducing pneumothorax, did not use a manometer, but determined that the needle was in the pleural cavity by instructing the patient to take deep breaths. An inrush of air occurring during inspiration indicated to him that the needle was in the proper position. At the second inflation upon a patient with extensive right-sided disease, the usual sound of inrushing air was missed. After two or three forced inspirations about three cubic inches (48 cc.) of nitrogen had been sucked in when the patient complained of feeling weak, became pale and fell into a state of collapse. Respirations were stertorous, the pulse slow and weak. The needle was withdrawn and stimulants administered. As soon as the pulse improved, a careful examination was made and revealed complete right-sided hemiplegia. When the patient became conscious he had aphasia. Within twenty-four hours paralysis of the face had disappeared. Some months later the face was normal, the leg weak and spastic, and the arm had regained but little power. During a refilling, while nitrogen was flowing in through the needle, one of Brauer's patients suddenly moved. She complained at once of great pain, became uncon-

scious, and collapsed. After several hours there was evident hemiplegia, and six hours after the operation the patient died. A patient in whom pneumothorax had been successfully induced was allowed to wait too long for refilling, and the gas had been almost completely absorbed. At the second operation, although no characteristic manometric variations occurred, it was supposed that the opening of the needle was in the pleural cavity. Thinking the needle might be plugged, a little nitrogen was allowed to run in. The patient immediately collapsed, and in a few minutes was dead.

It is needless for Brauer to say that to have personally lived through such an experience leaves an ineffaceable memory of its horror, and a grim determination to save no effort to avoid its repetition. It is on account of the danger of air embolism that he so insistently urges the use of his method, in spite of the difficulty for the operator and inconvenience for the patient.

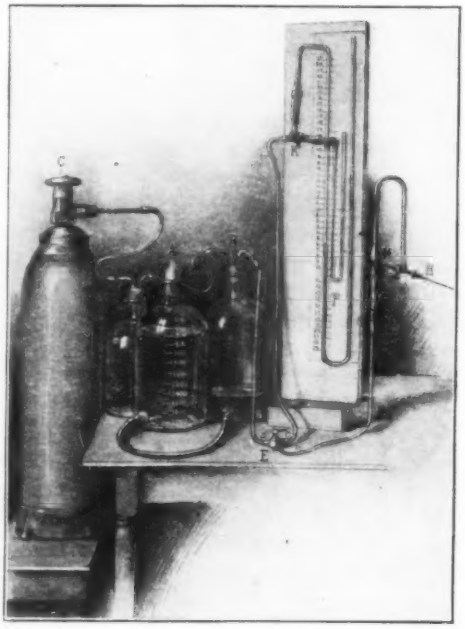
These unfortunate clinical results have not been reproduced experimentally. The lungs of healthy animals withstand, as Brauer himself asserts, a remarkable amount of trauma. He was unable to produce fatal air embolism in dogs, in spite of gross damage to the lung. However, operating with an aspirating needle, he found it impossible to reach the intrapleural space without producing some slight lesion of the visceral pleura. He believes that when the lung is diseased, even such trivial lesions may have serious consequences. Forlanini repeated these experiments. With great ease he could induce pneumothorax in dogs and upon forcibly inflating the lungs after removal from the body, rupture always occurred first about the borders, and never at the position corresponding with the point of operation.

It is well known that large amounts of air may be injected into the systemic circulation without producing fatal air embolism. If large amounts are rapidly injected into the veins, death occurs from dilatation of the right ventricle and cardiac syncope. Ten to twelve cubic centimeters of air per minute may be allowed to flow into a vein for an hour without producing any serious results. Fatal air embolism of the brain never follows the introduction of air into the systemic veins. Air introduced directly into the left ventricle or into the carotid artery produces immediately symptoms of cerebral embolism. Only very small amounts can be injected without danger. Forlanini finds that from six to eight cubic centimeters in the ventricle and from two to three cubic centimeters in the carotids may be safely given.

Simple puncture of the lung with an aspirating needle, even when the organ is diseased, is associated with little danger. Daily exploratory punctures are made without hesitation in all large medical clinics. Serious air embolism has followed attempts to produce pneumothorax only upon the injection of gas in the absence of satisfactory evidence that the needle is in the pleural cavity. We believe that when proper care is exercised the puncture method is quite safe, and in our hands it has given the utmost satisfaction. It is pertinent to note that of the four fatal cases reported by Brauer, the fatal case and instance of hemiplegia by Forlanini, and the instance of hemiplegia by Lemke, five of the seven serious complications occurred during secondary inflations. As the same method of refilling is used by all observers, Brauer's operative procedure does not remove the risk accompanying the subsequent injections.

The Method of Inducing Pneumothorax Used by the Authors.

The apparatus we have used is a modification of Brauer's. It is extremely simple, and the accompanying illustration shows its construction. Our earliest cases were inflated with air, later we employed nitrogen gas supplied, compressed in cylinders, by the Linde Air Products Co. *A* and *B* are bottles of two litre capacity, with outlets at the base connected with



rubber tubing. One of the bottles is graduated. Bottle *B* is fitted with a two-hole rubber stopper, into which two pieces of bent glass tubing are inserted. One of the tubes is connected with the nitrogen tank *C;* a wash bottle *D,* containing a 1 to 500 bichloride of mercury solution, is inserted between the bottle and the tank. The second tube is connected with a three-way stop-cock *E,* which in turn is connected through one arm with the manometer *F,* and through the other with the needle *H.* A sterile filter, *G* (a glass tube lightly packed with absorbent cotton), is inserted between the stop-cock and the needle. The manometer consists of two tubes, the outer for water, the inner for mercury. By means of the cock, *K,* the one desired may be connected with the instrument. The mercury manometer was added to be used under high pressure, but as we, in our work, have avoided high pressure, it is superfluous. The needle is fitted upon an attachment with a two-way stop-cock *M.* When the cock is turned transversely, the bore of the

needle is connected only with the lumen of the rubber tubing. When, as frequently happens, it is desired to clear the lumen of the needle, the cock may be turned and a wire introduced into the needle. The wire is bent so that its end will just reach, and not protrude beyond, the tip of the needle. Any desired degree of positive or negative pressure may be created in the system by elevating or lowering bottle *A*. When the handle of the stop-cock *E* is turned towards *a*, the bottle *B* is directly connected with the lumen of the needle *H*, and if bottle *A* be elevated, gas will flow through the needle. If the handle be turned to *b*, the lumen of the needle, *H*, is connected with the manometer *F*, and the pressure at the point of the needle recorded. If the handle be turned to *c*, the bottle *B* is connected with the manometer *F*, and the pressure in *B* registered.

Before beginning the operation, all of the tubing and stoppers are sterilized. Dry sterilization is best, for a few drops of water in the system will prevent the satisfactory registration of pressures. Of course the filter *G* is dry sterilized. The apparatus is then connected up, except that the tubing running from *b* to the needle is not added. The bottle *A* is then filled with warm bichloride solution (1 to 500) and elevated and the lever of the stop-cock *E* turned towards *a* so that the solution will flow from *A* into *B*. When *B* is completely filled, the lever is turned towards *b*. The system in the bottles is thus closed and *A* may be lowered without the solution in *B* running back. The cock upon the tank *C* is then carefully opened and as much gas (*N*) as may be desired is allowed to run in and displace the bichloride solution in *B*.

If a number of patients are to receive injections, whenever the gas in *B* has been used more may be added as desired, without disturbing any of the connections. When the operator is prepared to begin, he takes the two pieces of rubber tubing connecting the needle with the stop-cock from the sterile package and inserts the filter between them. An assistant slips one end of the tubing over the arm of the stop-cock, the operator connects the other with the needle. The wire is withdrawn from the needle and the cock turned transversely. To insure that the tubing is patent and the filter not too tightly packed, the lever of the three-way stop-cock *E* is turned to *c*. The manometer shows the pressure in *B*. If the lever be now turned to *b*, the pressure will fall at once to zero, if the tubing from *H* to *F* is free; if the needle or tubing is occluded, the pressure will not fall; if partially occluded the pressure falls slowly. The lever is then turned to *a* to insure that the gas from *B* flows freely through the needle, and is finally turned to *b*, and the operation begun with normal pressure in the needle connected with the manometer.

For the first inflation a blunt needle with rounded edge is used, a needle even less pointed than those usually employed for lumbar puncture. The bore of the needle should measure from 1 to 1.5 mm. in diameter, as smaller needles easily become plugged either with blood or bits of tissue, and transmit less satisfactorily the variation in pleural pressure. The point for operation having been selected, the skin is infiltrated with a weak solution of cocaine, and with a small scalpel the skin and subcutaneous tissues are punctured. The needle is introduced and carefully pushed obliquely forward into the interspace. Usually marked resistance is offered by the fascia of the intercostal muscles and the needle finally pierces it with a sudden pop, which is well felt and often heard. One is then sure that the point of the needle lies amongst the fibres of the intercostal muscle and another cautious advance forces it directly into the pleural space. The operator has the manometer before him, and if the pleura be not adherent, as soon as the point of the needle reaches the pleural space, the manometer records a marked negative pressure with wide respiratory variations. The extent of the variation depends upon the force of the respiratory efforts, usually equaling about minus 8 to minus 10 cm. water on inspiration, and minus 3 to minus 6 cm. on expiration.

When the pleural cavity is free from adhesions the operation invariably goes smoothly. When adhesions are present it is more complicated: (1) since the characteristic pleural variations in pressure are absent, and therefore one cannot tell with certainty when the needle is in the pleural space, and (2) collapse is rendered difficult and if the adhesions be dense, impossible. Various measures have been suggested to overcome these obstacles. Forlanini introduces the needle to a point where he thinks the pleural surface has been reached. He then very slowly and cautiously pushes the needle a little further in, and at each advance tests the position of the needle. For this purpose he compresses a small area of the rubber tubing between the fingers, thus forcing through the needle a very small amount of gas under high pressure. If the needle is in the extrapleural tissue the manometer will show a negative pressure equal to the amount of nitrogen expelled from the tubing. Should the gas vesicle be in close proximity to the pleura, respiratory variations may be recorded but they are usually small in extent. If the point of the needle is between the two layers of the pleura and the expelled gas separates them, a more marked negative pressure is recorded than could be accounted for by the amount of nitrogen injected and the respiratory variations are wider. If the needle is in the lung, the manometer oscillates with respiration but the mean pressure is about zero. If the needle is in the extrapleural tissue, or in a mass of dense pleural adhesions, the pressure rapidly rises, as gas is introduced in larger amounts, and gradually falls to normal as the gas diffuses throughout the tissue. Thus, in the instance of pleural adhesions emphysema of the connective tissue is produced instead of pneumothorax.

In the presence of adhesions Saugman introduces the needle into the lung. The oscillations of the manometer indicate its position. The needle is then cautiously withdrawn until the oscillations cease. With a syringe that fits into the end of the needle, aspiration is performed. If no blood is obtained, he forces in nitrogen under a pressure of from 20 to 30 cm. water. If the pleuræ separate, a well-marked negative pressure may occur after a few cubic centimeters of nitrogen have been injected. Larger amounts of gas may then be allowed to run in, although the operation is usually attended with great pain from the stretching and tearing of adhesions.

As we have stated, when the pleura is free, the operation of

inducing pneumothorax is extremely simple. We have, in a few instances, when we were confident that the needle was in the pleural cavity, attempted to break up adhesions by injecting air under pressure. After from 50 to 100 cc. of gas have been injected, the patient complains of extreme pain and the manometer registers a high, positive pressure, often 15 to 20 cm. water. During the following few minutes the pressure gradually falls to again rise as more gas is introduced. In this manner many hundred cubic centimeters may be injected, although the pleural surfaces remain adherent, and no pneumothorax is produced. We have, however, abandoned such ill-advised attempts. There is always danger of air embolism, and the infrequent success of efforts to forcibly separate an adherent pleura does not justify assuming the risk assumed. When we are unable to clearly find a pleural space, instead of manipulating the needle, we prefer to withdraw it and try in another position. The procedure gives so little discomfort to the patient that one does not hesitate to make numerous punctures in a search for a clear pleural space. In this way all danger of air embolism is avoided. In one of our cases we made three fruitless efforts in the axillary region to hit the pleural cavity, but the fourth, made in the back below the angle of the scapula, was successful. A partial pneumothorax was produced, which after subsequent refillings, extended and has become complete. In another instance eight attempts were made to induce pneumothorax, but to no avail. Another patient, in whom no pleural cavity could be demonstrated, was later operated upon by the Brauer method. The blunt canula entered a dense network of pleural adhesions and it was impossible to bring about a pneumothorax.

When adhesions are present and a small intrapleural air vesicle has been produced, Saugman advocated using high pressure to break up the adhesions. He for months maintained a pressure of from 20 to 30 cm. water in the cavity. If the adhesions are dense, it is impossible to separate the pleuræ and the method frequently produces unpleasant results. Subcutaneous emphysema spreading over the thorax and abdomen is not uncommon. Less often, but more serious in its consequences, air enters the loose connective tissue between the costal pleural and the thoracic fascia and reaches the mediastinum. It may appear in the subcutaneous tissue of the neck and cause great pain, and by pressure on the esophagus, difficulty in swallowing. Instances are reported in which the gas has pierced the diaphragm, probably in the connective tissue surrounding the aorta, and produced extensive subdiaphragmatic emphysema.

It is true that pleural adhesions frequently stretch, and under continued gentle pressure, allow the lung to completely collapse. If a fairly large air vesicle has been produced and the mediastinum is rigid, one may, with little discomfort to the patient, maintain an expiratory pressure of from 5 to 15 cm. of water, and note the gradual extension of the pneumothorax cavity and increasing collapse of the lung. There is always some, and often severe, pain where adhesions are attached.

If the adhesions are dense and, upon repeated punctures in different locations, no free pleural space can be found, it is wisest to abandon the attempt. Efforts to forcibly tear the adhesions under high pressure seldom succeed, and are attended by danger of air embolism and deep emphysema.

Pleural adhesions are then the main obstacle in the way of successfully inducing pneumothorax, and unfortunately their presence or absence cannot always be determined before the operation is undertaken. When the history of the illness points to frequent attacks of pleurisy, and particularly when physical signs indicate a thickened pleura, we are prepared for failure. When fluoroscopic examination and percussion on inspiration and expiration show a wide excursion of the lower lung border, we are equally confident that the operation will succeed. It is when the diaphragm movements are limited and there is no pleural dulness that definite predictions cannot be made. The diseased lung, as well as pleural adhesions, restricts movement, and while a lack of proportion between the extent of disease and the amount of restriction may be a valuable indication, we cannot be certain of the result. If compression of the lung has been begun by a pleural exudate, one may maintain and increase the collapse by withdrawing the fluid and introducing gas. As the pleural surfaces are already separated there is no difficulty in finding the space. When the gas is introduced through the effusion, we are deprived of the information afforded by the manometer, as the pressure variations are not transmitted through the fluid.

The amount of gas to introduce at the first inflation depends, in a measure, upon the condition of the patient. If severe pain or dyspnea develop, only a few hundred cubic centimeters should be injected, otherwise it is advisable to give from 500 to 800 cc. Forlanini and Saugman advocate giving from 100 to 200 cc. and very gradually, by daily repetitions, to increase the amount. They feel that, in this way, the contents of the chest adjust themselves more satisfactorily to the changing conditions of pressure. However, we believe the importance of at once producing an appreciable collapse of the lung, so that subsequent inflations may be carried on without danger of piercing the organ, far outweighs this consideration. As a matter of experience, from 500 to 800 cc. of gas may be introduced into the pleural cavity, even when the opposite lung is extensively diseased, without occasioning any unpleasant symptoms.

If the original inflation has been successful, the subsequent operations may be performed with great ease. A careful physical examination will usually indicate the position and extent of the pneumothorax, although X-ray examinations add wonderful precision to the observations. Stereoscopic plates, particularly, give an exact picture of the conditions and show the position of the lung and depth of the cavity at every point. For the second and subsequent injections a sharper needle of smaller bore may be used. If the lumen of the needle is free as soon as it enters the pleural space, the characteristic manometer oscillations occur and the gas should never be allowed to flow in if they are absent. When fine caliber needles are employed they frequently become plugged by a drop of blood or serum, or a bit of the subcutaneous fat. They may readily be cleaned by

introducing the obturator in the manner previously described. If the needle is in the pleural cavity, the manometer will then at once show respiratory variations and the gas is allowed to run in slowly under slight positive pressure. After each 100 cc. the pleural pressures are read, and the amount introduced largely regulated by the pressure conditions.

In the beginning inflations are made every second or third day. When the collapse is complete once a week suffices. Later, as the pleura loses its capacity for absorption, inflations at two and three-week intervals will maintain the collapse. At each inflation one estimates the amount of gas that has been absorbed by the amount necessary to bring the pleural pressure to the level of the end pressure of the previous inflation. Before collapse is complete, a few hundred cubic centimeters additional gas are added at each operation. Subsequently, if the pleural cavity is free, the pressure should be maintained that gives a slight positive elevation on inspiration. The normal pleural cavity absorbs from 80 to 100 cc. nitrogen per day; after the pneumothorax has existed for some months it absorbs from 25 to 50 cc. The pressure conditions vary somewhat in each individual case, and the amount of gas injected and the frequency of the inflations must depend absolutely upon the manometric record. When the pleural cavity is free it requires from four to five inflations before a positive pressure is reached. If adhesions are present, partly occluding the pleural cavity, a positive pressure may be recorded after the first inflation of from 500 to 800 cc. Under these conditions a moderate positive pressure is maintained, and not infrequently the adhesions will subsequently yield. The pressure records in Case 13, with a free pleural cavity, and in Case 15, with a partially adherent pleura, illustrate the points.

The pneumothorax may be maintained for a year or more and the lung be then allowed slowly to expand.

Throughout the whole procedure of inducing and maintaining pneumothorax, the manometer plays such an important part in guiding us that we shall briefly review the information it gives.

1. It indicates accurately when the needle has entered a free pleural space. The manometer at once records a negative pressure with marked respiratory variations.

2. When the needle is in the lung respiratory oscillations occur, but they vary about the zero point. If the patient draws a deep breath and holds it the manometer records a sudden negative pressure which quickly falls to normal. If the needle is in the pleural cavity, the negative pressure is maintained as long as the breath is held.

3. It indicates the size of the pleural space. If the pleura is free many hundred cubic centimeters of gas must be introduced before the pressure is raised. If the pleura is partially obliterated or the pneumothorax cavity walled off, 500 or 600 cc. of gas may bring the pressure to zero. If the cavity be small, a few hundred cubic centimeters may occasion a marked positive pressure. In walled-off spaces the respiratory variations are smaller than in the free pleural cavity.

4. If the needle be extrapleural or be imbedded in pleural adhesions, no respiratory variations occur. If a small amount of gas be injected the manometer records a high positive pressure, which gradually falls to zero as the gas diffuses.

5. It indicates the absorbing power of the pleura, and accurately controls the frequency and amount of injections necessary to maintain the desired conditions.

6. It indicates the degree of elasticity of the compressed lung. Upon subsequent refillings, if there is a very gradual rise in pressure following the introduction of each 100 cc. of gas, the lung has expanded with the diminishing pleural pressure. If the lung has remained collapsed, there is little rise in pressure following the introduction of the first few portions of gas, and then a very sudden and marked rise upon the introduction of a further small portion.

7. Likewise a slow increase in pressure with wide respiratory variations indicates a flexible mediastinum; a rapid increase in pressure with small respiratory variations, a rigid mediastinum.

8. v. Muralt has observed a sudden fall in pressure during inflation, due to the giving way of pleural adhesions. In another instance the lung ruptured during an inflation and the pressure fell at once to zero, and showed no subsequent rise even when large amounts of gas were introduced.

9. Occasionally, the manometer shows reverse respiratory oscillations; that is, a higher pressure with inspiration than expiration, due to paradoxical movements of the diaphragm.

The Pathological Anatomy of the Collapsed Lung.

Forlanini, Saugman, Graetz, Warnecke, and Kistler have published descriptions of the lung after months of collapse. When collapse has been complete the lung is a firm mass lying close to the spinal column. Histologically the following conditions are found:

1. The most striking change is the extreme fibrous tissue formation. This has been noted in every instance and occurs in a degree never observed under other conditions. Bronchi and alveoli may be compressed, and the scattered aveoli imbedded in the connective tissue give the organ the appearance of a gland. The overgrowth of connective tissue is more marked in the situations where compression has been complete, than in portions of the lung that have been prevented from collapsing by adhesions. A similar tendency to fibrous tissue formation is not observed in the opposite lung.

2. While evidence of advancing disease may be found in the opposite lung, the collapsed organ shows no fresh lesions. Old caseous areas may be seen surrounded by dense fibrous tissue, but no recent tuberculous infiltration.

3. The epithelium of the alveoli is transformed and becomes cuboidal or columnar in type.

4. The lymphatics are markedly dilated and pigment richly deposited.

Bruns, in an experimental study of the effects of pneumothorax, has shown that the amount of blood in the collapsed lung has decreased a few hours after the pneumothorax has formed and becomes less and less as collapse proceeds. Histologically he finds that in spite of long standing atelectasis,

the alveolar walls, although pressed together, display no tendency to adhere. The epithelium remains intact and the lungs may, at any time, be successfully reinflated. In the region of the large vessels and bronchi there is definite proliferation of connective tissue. The right side of the heart hypertrophies, consequent upon the interference with pulmonary circulation, although the diminished suction action of the lungs and diaphragm may play a part in its production.

Besides the functional rest that pneumothorax induces, there is, then, a decided tendency to fibrous tissue proliferation. The latter process may depend entirely, or in part, upon the altered circulatory conditions in the lung, and the occurrence of marked stasis in the lymphatic system.

The Clinical Symptoms of Induced Pneumothorax.

The effects of inducing pneumothorax upon the clinical symptoms may be divided into those resulting from the pneumothorax itself and the changes it occasions in the pre-existing symptoms. It is remarkable how well borne the procedure is, even by patients with advanced bilateral disease. If the pressure in the pleural cavity be raised only a little above zero and the patient be kept at rest, there is seldom more than a feeling of fulness in the chest and at times a little dyspnea. When complete collapse is obtained, if the opposite lung be unaffected, or but slightly diseased and grave constitutional symptoms are absent, patients even with a pressure of from 10 to 15 cc. of water do not suffer inconvenience, other than a little dyspnea on exertion. At the Eudowood Sanatorium they assist in household duties and in light work about the grounds. One of our patients (Case No. 3) is running a chicken farm near Baltimore and comes to the dispensary every two weeks for reinflation. He is not embarrassed in the performance of his work except when, as he says, he forgets and attempts to run. During the production of the pneumothorax pain is frequently complained of. When there is X-ray control, it is found that the pain is usually situated in the region of adhesions. We have frequently noted that epigastric pain follows early inflations, due, perhaps, to diaphraghmatic adhesions. In one instance an attack of pleurisy with effusion gave rise to severe pain. The usual view is that the pain of pleurisy is due to the rubbing together of the inflamed pleural surfaces. This patient had complete pulmonary collapse, and though apposition of the pleural surfaces was impossible, there was intense pain.

Upon the pre-existing symptoms pneumothorax has a striking effect. The cough and sputum may be increased for a few days, but they rapidly diminish after a few weeks, and completely disappear if the lung collapses fully and the opposite organ is unaffected or harbors a quiescent lesion. Nothing in the whole procedure is so striking as this effect upon the frequency of cough and the amount of sputum. Patients with from 50 to 100 cc. of expectoration per day may be almost sputum free three or four weeks after treatment is begun. Even when adhesions permit of only partial collapse of the lung, a diminution of the amount of sputum always occurs. As the sputum diminishes, the number of tubercle bacilli decreases and frequently bacilli entirely disappear. The temperature may be elevated above the previous level for a few days following the first injection, but thereafter rapidly falls and usually remains about the normal. With the decrease of fever the appetite increases and the general condition is markedly improved. At first there is almost constantly a loss of weight, which later is usually rapidly regained. Upon hemoptysis the procedure has a most beneficent influence. In a number of our cases hemoptysis promptly stopped after the first inflation. We recall the interesting instance of Schell. Rothschild has emphasized particularly this feature of the treatment.

With but a small number of cases it is impossible to express the results of the treatment numerically. The character of the cases varies so widely that statistical studies would permit no respectable inference. For a time, at least, the results obtained in individual instances must be used to fortify the claims made for the method. For this reason we add the records, in sufficient detail, of the twenty patients upon whom we have induced pneumothorax and summarize our results and present our impressions.

Review of Cases.

Since all the cases here reported were suffering from moderately or far advanced pulmonary tuberculosis, it would be futile to gauge the value of pneumothorax treatment by classifying them according to the stage of the disease. As we have insisted, a just estimate of the value of the treatment may be gained only by a study of the individual instance. However, some general grouping is desirable and therefore we divide the cases according to the success attending our efforts to produce collapse of the diseased lung. There are four groups:

I. In three instances (Cases 5, 10, and 17) induction of pneumothorax was followed by death or a serious complication.

II. In three instances (Cases 6, 7, and 14) it was impossibe to produce pneumothorax.

III. In seven instances (Cases 2, 4, 8, 11, 15, 16, and 18) only an incomplete pneumothorax was produced.

IV. In seven instances (Cases 1, 3, 9, 12, 13, 19, and 20) a complete pneumothorax was produced.

Group I.—Case 5, with extensive pulmonary tuberculosis and pleural effusion, developed a pyopneumothorax after the first inflation. While it is possible that the infection of the exudate may have come from the lung it seems more likely that it depended upon a faulty operative technic. The symptoms following the injection overshadowed any favorable influence the pneumothorax may have exercised and treatment was promptly abandoned.

Case 10 developed evident symptoms of tuberculous meningitis after the third inflation, followed by death fourteen days later. Tuberculous meningitis is not an uncommon terminal event in pulmonary tuberculosis and we are disinclined to allow that the pneumothorax was responsible for its occurrence.

A definite conclusion cannot be reached, but if the pneumothorax was the direct cause, the mechanism by which the meningitis was produced is not easy to explain.

Case 17 was in a desperate condition when treatment was begun. Only two inflations were given, the patient dying 10 days after beginning the treatment. The pneumothorax lessened the cough. We are convinced that the treatment did not hasten the patient's death.

Group II.—In Cases 6 and 14 no pneumothorax could be produced, owing to the pleural adhesions. In Case 6 the Forlanini and the Brauer methods both were fruitlessly employed, and in Case 14 five attempts in different positions were made without success. In Case 7, although we were able at each operation to introduce a few hundred cubic centimeters of gas, the immediate rapid rise of pressure after the introduction of small amounts of gas followed by a gradual fall to normal, and the absence of satisfactory respiratory variations in pressure indicate that no true pleural space was formed, the gas diffusing through the pleural adhesions. The course of the disease in these three cases was entirely uninfluenced by the treatment.

Group III.—As stated in the text, Cases 2 and 4 were hopelessly advanced when the treatment was instituted. Under the most favorable conditions they were rapidly going down hill. The treatment was begun at their request, and on our part with the desire to demonstrate the harmlessness of the procedure rather than with the expectation of obtaining any permanent benefit. The cases are interesting as examples of patients with extreme bilateral pulmonary involvement displaying little distress, although there was extensive collapse of one lung with an expiratory pleural pressure of 7 cc. of water and marked dislocation of the mediastinum. The condition is in striking contrast to the clinical picture after spontaneous pneumothorax in advanced pulmonary tuberculosis. In both cases there was reduction of cough and sputum, but the general condition was uninfluenced and the disease continued to progress.

In the other five cases in this group one lung was totally or almost totally involved, and there was a definite but not extensive lesion of the other lung. In four cases the right lung was more extensively involved than the left; in Case 18 the reverse was true. In all five the upper lobe was the seat of the most marked lesion, and it was adhesions over the upper lobe that prevented complete collapse. In Cases 8, 16, and 18 the production of pneumothorax was followed by diminution of the cough and amount of sputum. In Case 11 there was gradual lessening of cough and sputum, marked reduction not occurring until after the advent of the pleural effusion. The effect upon hemoptysis in Case 16 is noteworthy. In Case 15 the sputum was a little decreased but the cough was aggravated.

Three of the patients showed marked improvement in their general condition and in the constitutional symptoms (Cases 8, 11, and 16). In Case 15 treatment was abandoned and Case 18 was under observation only a short time. We wish to call particular attention to the improvement in Case 8.

Group IV.—In all seven cases there was well marked disease of one lung, with some involvement of the opposite. In the three Cases 3, 13 and 20 the right lung was the more severely diseased; in four Cases 1, 9, 12, and 19 the left. In all seven cases pneumothorax was followed by a diminution of cough and expectoration. Six of the seven cases (all save No. 1) had hemoptysis of varying grade, which did not recur after the pneumothorax was complete. All of the patients showed marked improvement in their general condition except Case 9, who lost considerable weight but was otherwise well. In Case 12 the disease progressed somewhat in the opposite lung. Cases 19 and 20 were under observation but a short time. Cases 1, 12 and 13 developed pleurisy with effusion. We wish to call special attention to the excellent recoveries made by Cases 1, 3, and 13.

CONCLUSIONS.

1. Induced pneumothorax is a harmless procedure and the operation, carefully performed, is without danger.

2. In 3 out of 20 cases it was impossible to produce any pulmonary collapse owing to general pleural adhesions.

3. Of 16 cases in which pneumothorax was successfully produced, in but 7 was the pneumothorax complete.

4. Of 9 cases with induced pneumothorax existing for four months or longer 4 have developed pleurisy with effusion.

5. The pneumothorax has, in most instances, an immediate and striking influence upon the cough and expectoration. Tubercle bacilli may disappear from the sputum.

6. Constitutional symptoms abate more slowly. In most instances there is at first a loss in weight followed by a gradual rise.

7. The total collapse of one lung causes surprisingly little inconvenience. Usually there is but slight dyspnea on exertion. Many of the patients with an induced pneumothorax assist actively in the work about the sanatorium.

8. The procedure is of great value in the treatment of pulmonary hemorrhage.

9. While induced pneumothorax will never become a routine method for the treatment of pulmonary tuberculosis, still in selected cases it offers a prospect of temporary and permanent relief when the usual methods of treatment have been unsuccessfully tried. Quiescent lesions in one lung with acute recrudescence in the other are the most favorable for the treatment. Its use need by no means be limited to strictly unilateral lesions, but when there is advanced disease of both lungs little benefit can be expected. It would seem advisable not to withhold the treatment until the patient is hopelessly advanced, but to apply it judiciously to suitable moderately advanced patients in whom the disease tends to progress in spite of appropriate treatment.

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NOTES ON NEW BOOKS.

The Sexual Life of the Child. By DR. ALBERT MOLL. Translated from the German by DR. EDEN PAUL. $1.75. (*New York: The Macmillan Company, 1912.*)

This is an attempt at the study of individual psychosexual development, normal and abnormal from infancy to maturity. The material is from the author's large personal observation of cases and these case histories, with numerous well-chosen citations from the literature and comments thereon make the bulk of the book.

However, satisfactory explanation of the phenomena described is entirely lacking. The work of Freud, Jung, Stekel and others, which has thrown so much light on the psychology of the unconscious, is practically unknown to the author, though some of Freud's earlier work is mentioned only to be firmly disagreed with, probably largely because of obvious misunderstanding of it. The statement (p. 14) that "in any case, Freud has not systematically studied the individual manifestations of the sexual life of the child," is amusing. The authors "analysis of the phobia of a 5-year-old boy" covers 105 pages in the 1909 Bleuler-Freud Jahrbuch. The result then is a book of valuable source data, only, and one misses (1) an adequate hypothesis, psychologic or biologic, concerning the nature of the sex impulse, and (2) a conception of the mental mechanisms underlying the manifestations of the sex impulse, which would reconcile the contradictions and show the organic unity of them.

It will serve, however, to draw attention to the neglect of sex instruction, and the serious results of that neglect in children and youth, and emphasize the need, now being more widely recognized daily, of very radical change in hygienic and pedagogic customs in that respect.

Diseases of the Mouth for Physicians, Dentists, Medical and Dental Students. By PROF. DR. F. ZINSSER, Cologne. Translated and Edited by JOHN BETHUNE STEIN, M. D., New York. Illustrated. $7.00. (*New York: Rebman Company, 1912.*)

The title of this work is misleading, for it deals only with syphilis and similar diseases of the mouth. It is, as such, an excellent contribution to the study of these diseases. The author makes no attempt to treat the whole subject of syphilis, but only as it shows itself in the mouth. The colored illustrations, made from moulages in the collection of Dr. Zinsser are splendid, and each plate, fifty-two in number, is faced by a brief description of the lesion shown. The introductory chapter is brief but furnishes a clear account of syphilis as it is met with in the mouth, and the translation runs smoothly. It is, however, the illustrations which make this work especially serviceable. There are few institutions in this country that have collections of moulages, from which the best reproductions are secured, and, therefore, the publishers are to be thanked for having published this work in English with such admirably reproduced illustrations.

Nervöse Angstzustände und Ihre Behandlung. Von DR. WILHELM STEKEL (Wien). Zweite, Vermehrte und Verbesserte Auflage. $4.25. (*Berlin and Wien: Urban u. Schwarzenberg; New York: Rebman Company, 1912.*)

The users of psychoanalysis, as developed by Freud, his pupils and followers, will find this a useful book to add to their library on this subject. Dr. Stekel divides these conditions of anxiety into two classes, a neurosis (*Angstneurose*) and hysteria (*Angsthysteric*). Under the neuroses he classifies respiratory and cardiac distress, disturbances of digestion, including nausea and vomiting of pregnancy, congestion, loss of consciousness, fainting, trembling, shivering, paræsthesias, cramps, tics, pains and sleeplessness. Under hysteria he classes those cases with obsession, topophobia, blushing, anxiety about travelling in railroads, and examinations, psychical impotency, dizziness and anxiety of high places, stuttering, hypochondria, etc. Where the conditions are often so similar, and where the division is purely arbitrary, careful study alone of individual cases will teach the student whether an individual is suffering from a neurosis or hysteria. The use of psychoanalysis in the elucidation of these troubles requires much time and patience and should only be undertaken by those who are fully acquainted with the responsibility of its employment. Stekel's work will serve not only as a guide to its proper use, but incidentally to a further study of the troubling symptoms he treats by this modern method, which like all new modes of therapy has yet to find its correct place among our means of cure.

Diagnose und Therapie der Magen und Darmkrankheiten. Von PRIVATDOZENTEN, DR. WALTER ZWEIG. Zweite, vermehrte Auflage. Illustrirt. $4.00. (*Berlin und Wien: Urban & Schwarzenberg; New York: Rebman Company, 1912.*)

Written by a pupil of Boas for the general practitioner this book met with approval in its first edition, and should meet with like approbation in its revised form. The author has added a few chapters which somewhat enlarge its scope but do not alter its excellence as a guide to the study and knowledge of diseases of

the gastro-intestinal tract. The first part is general in character, dealing with the physiology of digestion, cures, physical treatment, and that by drugs, etc., while the latter two-thirds of the work is devoted to the diseases of the stomach and intestines, as follows: Acute and chronic gastritis, ulcer, dilatation, cancer, entroptosis, nervous dyspepsia, acute and chronic enteritis, chronic ulcerative colitis, sigmoiditis, chronic obstipation, ulcers, cancer, appendicitis, diseases of the large intestine, ileus, and nervous diseases of the intestine. The final chapter describes concisely the chemical and microscopical examination of the gastric contents and fæces. Those who can read German will find Dr. Zweig's work conservative and helpful.

Life and Letters of Dr. William Beaumont, including hitherto Unpublished Data Concerning the Case of Alexis St. Martin. By JESSE S. MYER, A. B., M. D., Associate in Medicine in Washington University, St. Louis. With an Introduction by SIR WILLIAM OSLER, Bt., M. D., F. R. S. Regius Professor of Medicine in Oxford University, England. With 58 illustrations. (*St. Louis: C. V. Mosby Company, 1912.*)

The author explains that the appearance of this book at the present time is to commemorate the hundredth anniversary of William Beaumont's entrance upon the practice of medicine. Upon June 12, 1812, he was licensed in Vermont to practice "physic and surgery."

The book before us is an effort on the part of the author to portray Beaumont not only as a man of science but as a man of forceful personality with peculiar traits of character. The labor of ascertaining the facts of the life of one who lived for many years upon the frontier as an army surgeon has been very great and the author is to be congratulated upon his thorough and conscientious work. The result has been a complete and final biography of a no ordinary man. He had a talent for research and accomplished remarkable results when his period and the difficulties which he encountered in his self-imposed tasks are considered. Had the same opportunity been afforded today to modern investigators for the first time how many would have made more important discoveries than he did respecting gastric secretion? The physiology of digestion, according to Dr. Osler, owes to him the following: "The confirmation of the discovery by Prout of the presence of hydrochloric acid in the gastric juice; the recognition that the essential elements of the gastric juice and the mucous secretion were separate; the establishment by direct observation of the profound influence of mental disturbances on the secretion of the gastric juice and on digestion; the fuller and more accurate comparative study of digestion in the stomach with digestion outside the body; the rapid disappearance of water from the stomach through the pylorus; the first comprehensive and full study of the movements of the stomach; the study of the digestibility of different articles of diet, which remains to-day one of the most important contributions ever made to practical dietetics; the relation between the amount of food taken and the quantity of gastric juice secreted; and many other points, the true significance of which have not been recognized until the recent researches of Professor Pavlow."

Born in Lebanon, Conn., in 1785 he obtained a common school education and at the age of 21 years with "a horse and cutter, a barrel of cider and $100 in hard-earned money" he left home and entered upon the work of teaching at Champlain, New York, where he remained for three years. In 1810 he entered upon the study of medicine as an apprentice with a preceptor at St. Albans, Vt., and received his license to practice in June, 1812, as has been already stated. In the following September he became a surgeon's mate (assistant surgeon) and received a commission from President Madison. He served during the War of 1812 and participated in several battles. In 1816 he removed to Plattsburgh and engaged in general practice there until about 1820 when he re-entered the U. S. Army and was ordered to Fort Mackinac. In June, 1822, Alexis St. Martin was seen by him a few minutes after he received the wound which opened the interior of his stomach to scientific study and for many years afterwards was a source of solicitude to him. The story of Beaumont's trials with his wayward patient, his struggles and his triumphs, his disappointments and his heavy responsibilities in caring for St. Martin and his family is vividly told. The surgeon general at first gave him some assistance it is true, but the burden for the most part was borne by Beaumont alone and when an unfriendly surgeon general assumed office he was finally forced to resign from the army corps after a service of more than twenty-five years. During the remaining thirteen years of his life he lived in St. Louis and was an honored and influential citizen.

The book should be read by all who are interested in the struggles, disappointments and achievements of medical men. The author has done his work well and deserves the thanks of all physicians.

P. Blackiston's Son & Co. (Philadelphia) have just issued their pocket Visiting List for 1913, useful for the country practitioner and others. The fact that it is already in its 62d year shows how popular it is. It contains its usual tables of incompatibility, antidotes for poisons, doses, etc., and rules for treating asphyxia and apnœa. Its size is convenient and its make-up neat. Price $1.25.

The Practitioner's Encyclopædia of Medicine and Surgery in all their Branches. Edited by J. KEOGH MURPHY, F. R. C. S. $7.00. (*London: Henry Frowde and Hodder & Stoughton, 1912.*)

While it is fair to question the value and importance of such an encyclopædia, it is only just also to begin by complimenting the editor highly on having produced such an excellent work. The quality of the articles is remarkably good, and as a whole any future editor will have a difficult task before him if he desires to compete with this work, which is practical and simple—details of unusual surgical operations and pathological and anatomical data in the main being omitted, but otherwise the practitioner will find a general résumé of any medical subject upon which he may want information.

Almost all branches of science have their encyclopædias to-day and so it is natural that medicine should have its own, but how many doctors will really find this book useful? It is surprising the number of good text-books that are to be found in any young physician's library, and with these he can do better than with an encyclopædia. A five-foot shelf will hold almost all the text-books that are essential. Of course the price of this book makes it attractive. It would be still more useful did the authors of the various articles give a few references to standard works, for, supposing a young physician is called upon to give advice on the construction or management of a hospital, the article in the encyclopædia will give him only the elementary principles and he will want to look further and will be without a guide.

The division of articles so that there are long chapters on syphilis under both medicine and surgery makes the volume unnecessarily large. One comprehensive article on the subject could have been written by two men together, or by one alone and this reflection applies to other chapters as well.

It is to be noted that the paging of the contents is faulty; and that the index is incomplete as for instance there is no reference to enteric fever; scarlet or measles is not to be found under fever; under both typhoid and syphilis there is no reference to the main article; and none to the occurrence of fever in syphilis. There are a few illustrations in the volume which might as well have been omitted since many others of equal value find no place.

There should be more or none and this is equally true of the prescriptions which occur scattered throughout the volume without much rhyme or reason.

These imperfections do not seriously affect the value of this work and are drawn attention to merely that they may be corrected in a future edition. We welcome the encyclopædia as a thorough and trustworthy book of reference and hope Dr. Murphy's energy in putting it through will be rewarded by its meeting with a hearty welcome by the profession.

Diagnostic and Therapeutic Technic. By A. S. MORROW, M. D. $5.00. (*Philadelphia and London: W. B. Saunders & Co., 1911.*)

No question should arise as to whether or not the hospital interne or practitioner should learn the technic of exploratory punctures, aspirations, and the minor surgery of medicine from experience. Certain it is that the technic of many of the diagnostic and therapeutic measures can be acquired only in a practical way. The responsibility of previous enlightenment rests with the teachers of medicine who give from their experience. However, the most experienced will find opportunity to refer to such a unique volume as Morrow's Diagnostic and Therapeutic Technic.

The field covered is as comprehensive as the title, and each procedure is described with most careful detail of indications and contraindications, apparatus, choice of methods, results, and possible accidents. General and local anæsthesia are given one hundred pages of consideration, to which very little more could be added as to technic. Such chapters as Sphygmomanometry Bier's Hyperæmic Treatment and the Collection and Preservation of Pathological Material, seem decidedly out of place. Indeed, much has been included which would preferably be sought in publications of the eye, ear, nose and throat, gastro-intestinal, genito-urinary, and gynecological specialists.

Most helpful are the chapters upon Transfusions, Infusions, Hypodermoclysis, and Venesection. Such subjects as vaccination and administration of antidiphtheric serum are appropriately handled. In fact, throughout the book technic is very satisfactorily described in detail. In this the volume fulfills its purpose and supplies a great need. So far as I know, there is no similar effort in the over-abundant supply of medical text-books.

The illustrations are necessarily diagrammatic. Some points of value are missed. For instance, for lumbar puncture the patient is "placed upon his left side." This would be convenient for a left-handed operator, but decidedly awkward for the majority. Again, no emphasis is laid upon the all-important point of having the spine straight, so difficult to obtain in the average bed. In such a complete consideration of the subject, it seems odd that no mention is made of the great value of the simple, three-way stop-cock which may be attached to any threaded syringe, converting it into a most useful instrument for withdrawal or introduction of fluids.

Physical diagnostic methods and clinical microscopy are included, but too briefly, of course, to be of any value.

If the author had adhered strictly to the title, the volume could have been reduced one-third and brought the price perhaps within the reach of more who need the technic.

A Practical Hand-book of the Diseases of the Ear. By WILLIAM MILLIGAN, M. D. and WYATT WINGRAVE, M. D. Illustrated. $5.00. (*London: Macmillan & Co., Ltd., 1911.*)

We regard this work as the best of the English text-books on diseases of the ear.

The subject matter is clearly and briefly presented. All the modern methods of diagnosis and treatment are mentioned, together with references to the more important original articles.

The value of the book is greatly enhanced by the chapter by J. Purves Stewart, on Diseases of the Ear in Relation to General Medicine. This chapter contains a brief, concise summary of the lesions of the nervous system which produce auditory disturbances together with a description of the more striking auditory phenomena which form a part of the clinical picture.

The treatment of the nose and noso-pharyngeal mucosa is very properly insisted upon (page 194), and the authors have greatly added to the value of the work by giving, in Chapters XL-XLIV, an admirable resumé of the conditions of the throat, nose, and naso-pharynx which may be primarily responsible for otological diseases.

The suppurative otological diseases, with their complications and sequellæ, are discussed in detail, and quite properly so, since the recognition and treatment of such conditions is of the greatest importance to practitioners and surgeons alike.

Dr. Milligan has made tuberculosis of the middle ear and temporal bone one of his special studies, and the chapter on this subject forms a valuable monograph.

The book is particularly attractive because it is something more than a mere "rehash" of other text-books and manuals; it contains a large amount of original work and many references for those wishing further information.

A Treatise on Pellagra for the General Practitioner. By EDWARD JENNER WOOD, M. D. Illustrated. (*New York and London: D. Appleton and Company.*)

There is to-day no reason why physicians in this country should not have a clear mental picture of this disease, even though they may have met with no cases. In addition to the translation of Marie's work, both Roberts and Niles have written treatises on Pellagra, and now Wood adds his to the series. There are also valuable reports from some of the southern states' boards of health, and numerous articles in the current literature which are of avail to the student interested in this new American problem. The disease is a far reaching one and while most prevalent in the south, yet sporadic cases are turning up all through the United States. Until we know the cause of this disease it is all important that these cases should be recognized, for if they are due to some organism the patients must be most carefully watched as they may prove to be carriers of disease which like malaria may be transmitted through the bite of some insect. If, however, the malady is due to some chemical process it will not be necessary to isolate these patients. Wood is a supporter of this newer theory of infection, rather than the older one which holds that the disease is due to mouldy corn. But the proof that the bite of a fly is accountable for pelagra is, as yet, far from convincing; and it will require the continued work of many students of the problem before the obscure cause is finally found. Dr. Wood has written an interesting work, illustrated by some excellent photographs; his presentation of the disease in its various forms is thorough and his monograph will, it is certain, remain for some time the standard work in English; but the other works referred to all have points of excellence and are needed for a compicter study of the entire question.

The Surgical Clinics of John B. Murphy, M. D. October, 1912. Vol. I, No. 5. (*Philadelphia and London: W. B. Saunders Company.*)

There are eighteen different surgical subjects discussed in this number. Such talks as these at the operating table prevent a subject from being treated in a thorough manner, but they often bring out points, which are important and which are frequently overlooked in a more carefully prepared lecture as being trivial. It is from this point of view that students will find the reading of these clinics interesting.

The History of the Prison Psychoses. By Drs. Paul Nitsche and Karl Williams. Translated by Frances M. Barnes, Jr., M. D. and Bernard Glueck, M. D. (*New York: The Journal of Nervous and Mental Disease Publishing Company, 1912.*)

This is the latest monograph of the important series published by the above named company, and is an interesting survey of the development of the modern German views on prison psychoses. Prison physicians and others called to examine persons detained in our station houses and jails will find this historical review an aid in determining how best to classify some poor mentally impaired prisoner. The translation has been well done.

The Care of the Body. By R. S. Woodworth. $1.50. (*New York: The Macmillan Company, 1912.*)

Mr. Woodworth's book is written as a guide on personal hygiene for young men, and is well adapted to its end. The instruction given is simple, and can be easily comprehended by any intelligent youth although he has not studied medicine. It may be safely recommended, and will be of real service in schools and elsewhere. To-day more than ever before the public is being educated in all matters relating to health, and such a book as this will help to advance the good work that is being done along these lines.

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